=> fil medl drugu ipa wpix biosis embase; d que l14; fil capl; d que l1
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Inventor search

L9 44 SEA FREDDO J?/AU
L10 2512 SEA HU LOWE D?/AU OR HULOWE D?/AU OR LOWE D?/AU
L11 81 SEA KERSI PITHAVALA Y?/AU OR PITHAVALA Y?/AU
L12 17 SEA STEINFELDT H?/AU
L14 13 SEA (L9 AND (L10 OR L11 OR L12)) OR (L10 AND (L11 OR L12)) OR (L11 AND L12)

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FILE LAST UPDATED: 9 Aug 2006 (20060809/ED)

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L1 1 SEA FILE=CAPLUS ABB=ON US2004-816242/AP

=> dup rem l1,l14
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FILE 'DRUGU' ENTERED AT 12:16:38 ON 10 AUG 2006

FILE 'WPIX' ENTERED AT 12:16:38 ON 10 AUG 2006

FILE 'BIOSIS' ENTERED AT 12:16:38 ON 10 AUG 2006

FILE 'EMBASE' ENTERED AT 12:16:38 ON 10 AUG 2006

PROCESSING COMPLETED FOR L1
PROCESSING COMPLETED FOR L14
L15 9 DUP REM L1 L14 (5 DUPLICATES REMOVED)
ANSWER '1' FROM FILE CAPLUS
ANSWERS '2-4' FROM FILE MEDLINE
ANSWERS '5-8' FROM FILE DRUGU
ANSWER '9' FROM FILE BIOSIS

=> d ibib ed abs 1; d iall 2-9

L15 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:857398 CAPLUS
DOCUMENT NUMBER: 141:337772
TITLE: Pharmaceutical dosage forms comprising AG 013736
INVENTOR(S): Freddo, James Lawrence; Hu-Lowe, Dana; Pithavala, Yazdi Kersi; Steinfeldt, Heidi Marie
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087152	A1	20041014	WO 2004-IB867	20040317
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004226586	A1	20041014	AU 2004-226586	20040317
CA 2520932	AA	20041014	CA 2004-2520932	20040317
EP 1613320	A1	20060111	EP 2004-721255	20040317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
BR 2004009230	A	20060328	BR 2004-9230	20040317

US 2004224988	A1	20041111	US 2004-816242		20040401 <--
NL 1025873	A1	20041005	NL 2004-1025873		20040402
NL 1025873	C2	20060214			
NO 2005005143	A	20060103	NO 2005-5143		20051102
PRIORITY APPLN. INFO.:			US 2003-460695P	P	20030403
			US 2003-491771P	P	20030731
			WO 2004-IB867	A	20040317

ED Entered STN: 18 Oct 2004

AB The invention provides pharmaceutical dosage forms of AG 013736 or salts, solvates or prodrugs. The invention further provides methods of treating abnormal cell growth, such as cancers, by administering the dosage forms to a mammal. A high-dose combination therapy of AG 013736 ad docetaxel generates greater delay of primary tumor growth and metastasis than either monotherapy alone.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2006347111 IN-PROCESS

DOCUMENT NUMBER: PubMed ID: 16332390

TITLE: The anti-angiogenesis agent, AG-013736, has minimal activity in elderly patients with poor prognosis acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

AUTHOR: Giles Francis J; Bellamy William T; Estrov Zeev; O'Brien Susan M; Verstovsek Srdan; Ravandi Farhad; Beran Miloslav; Bycott Paul; **Pithavala Yazdi**; **Steinfeldt Heidi**; Reich Steven D; List Alan F; Yee Karen W L

CORPORATE SOURCE: Department of Leukemia, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 428, Houston, TX 77030, USA.. frankgiles@aol.com

SOURCE: Leukemia research, (2006 Jul) Vol. 30, No. 7, pp. 801-11. Electronic Publication: 2005-12-05. Journal code: 7706787. ISSN: 0145-2126.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 9 Jun 2006
Last Updated on STN: 19 Jul 2006

ABSTRACT:
AG-013736 is an oral anti-angiogenesis agent with activity against a variety of receptor tyrosine kinases, including VEGFR-1, VEGFR-2, VEGFR-3, c-kit, and PDGFR-beta. A phase 2 study was conducted in patients with poor prognosis AML or MDS. Twelve patients (six AML; six MDS) were treated with AG-013736 at a dose of 10mg orally daily for a median of 56 days (range, 1-248 days). Median age was 80 years (range, 58-88 years). Grade 3 or 4 drug-related toxicities included hypertension (42%), mucositis (8%) and deep venous thrombosis (8%). No objective responses occurred; two patients with MDS had stable disease for 8.3 and 6.2 months, respectively. Bone marrow expression of VEGFR-1 and VEGFR-2 was observed in 11% and 0% of patients, respectively. Sustained decreases in soluble VEGFR-2 plasma levels with concomitant elevation in plasma VEGF and placental growth factor levels were obtained during the course of therapy with AG-013736. AG-01736 had minimal biologic or clinical activity in this elderly patient population.

L15 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2005442884 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16027439
TITLE: Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results.
AUTHOR: Rugo Hope S; Herbst Roy S; Liu Glenn; Park John W; Kies Merrill S; **Steinfeldt Heidi M**; **Pithavala Yazdi K**; Reich Steven D; **Freddo James L**; Wilding George
CORPORATE SOURCE: University of California, San Francisco Comprehensive Cancer Center, USA.
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2005 Aug 20) Vol. 23, No. 24, pp. 5474-83. Electronic Publication: 2005-07-18.
Journal code: 8309333. ISSN: 0732-183X.
COMMENT: Comment in: J Clin Oncol. 2005 Aug 20;23(24):5417-9. PubMed ID: 16027435
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 20 Aug 2005
Last Updated on STN: 24 Sep 2005
Entered Medline: 23 Sep 2005

ABSTRACT:
PURPOSE: We studied the safety, clinical activity, and pharmacokinetics (PK) of AG-013736, an oral receptor tyrosine kinase inhibitor of vascular endothelial cell growth factor, platelet-derived growth factor, and c-Kit, in patients with advanced cancer. PATIENTS AND METHODS: Patients received fixed doses of AG-013736 orally in 28-day cycles. In the first cohort, patients initially received two single test doses of AG-013736 (10 and 30 mg); subsequent dosing was determined by individual PK parameters. Doses in subsequent cohorts were assigned by using a traditional dose-escalation/de-escalation rule based on observed toxicities in the current and previous cohorts. PK analysis included evaluation of the effect of food and antacid. RESULTS: Thirty-six patients received AG-013736 at doses ranging from 5 to 30 mg by mouth twice daily. The dose-limiting toxicities observed included hypertension, hemoptysis, and stomatitis and were seen primarily at the higher dose levels. The observed hypertension was manageable with medication. Stomatitis was generally tolerable and managed by dose reduction or drug holidays. AG-013736 was absorbed rapidly, with peak plasma concentrations observed within 2 to 6 hours after dosing. The maximum-tolerated dose and recommended phase II dose of AG-013736 is 5 mg, twice daily, administered in the fasted state. No significant drug interaction with antacid was seen. There were three confirmed partial responses and other evidence of clinical activity. CONCLUSION: In this study, we have demonstrated clinical activity and safety of AG-013736 in patients with advanced solid tumors and identified the dose for phase II testing. The unique phase I study design allowed early identification of important absorption and metabolic issues critical to phase II testing of this agent.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Oral
Adult
Aged
*Angiogenesis Inhibitors: AD, administration & dosage
Angiogenesis Inhibitors: AE, adverse effects

*Angiogenesis Inhibitors: PK, pharmacokinetics
Area Under Curve
Drug Administration Schedule
Drug Interactions
Humans
*Indazoles: AD, administration & dosage
Indazoles: AE, adverse effects
*Indazoles: PK, pharmacokinetics
Maximum Tolerated Dose
Middle Aged
Neoplasms: BL, blood
*Neoplasms: DT, drug therapy
*Neovascularization, Pathologic: DT, drug therapy
Research Support, Non-U.S. Gov't
Treatment Outcome

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Indazoles); 0 (axitinib)

L15 ANSWER 4 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2005442885 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16027440
TITLE: Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: results from a phase I study.
AUTHOR: Liu Glenn; Rugo Hope S; Wilding George; McShane Teresa M; Evelhoch Jeffrey L; Ng Chaan; Jackson Edward; Kelcz Frederick; Yeh Benjamin M; Lee Fred T Jr; Charnsangavej Chusilp; Park John W; Ashton Edward A; **Steinfeldt Heidi M**; **Pithavala Yazdi K**; Reich Steven D; Herbst Roy S
CORPORATE SOURCE: University of Wisconsin Comprehensive Cancer Center, Madison, WI, USA.
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2005 Aug 20) Vol. 23, No. 24, pp. 5464-73. Electronic Publication: 2005-07-18.
Journal code: 8309333. ISSN: 0732-183X.
COMMENT: Comment in: J Clin Oncol. 2005 Aug 20;23(24):5417-9. PubMed ID: 16027435
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 20 Aug 2005
Last Updated on STN: 24 Sep 2005
Entered Medline: 23 Sep 2005

ABSTRACT:
PURPOSE: Identifying suitable markers of biologic activity is important when assessing novel compounds such as angiogenesis inhibitors to optimize the dose and schedule of therapy. Here we present the pharmacodynamic response to acute dosing of AG-013736 measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). PATIENTS AND METHODS: Thirty-six patients with advanced solid tumors were treated with various doses of AG-013736. In addition to standard measures of objective disease response and pharmacokinetic analysis, DCE-MRI scans were acquired at baseline and repeated at cycle 1--day 2 after the scheduled morning dose of the AG-013736 in 26 patients. Indicators of a

vascular response, such as the volume transfer constant (K(trans)) and initial area under the curve (IAUC), were calculated to assess the effect of treatment on tumor vascular function. RESULTS: Evaluable vascular response data were obtained in 17 (65%) of 26 patients. A linear correlation was found in which the percentage change from baseline to day 2 in K(trans) and IAUC was inversely proportional to AG-013736 exposure. Using a conservative a priori assumption that a > or = 50% decrease in K(trans) was indicative of an objective vascular response, a 50% decrease in K(trans) was achieved and corresponded to a plasma AUC(0-24) of > 200 ng . h/mL. CONCLUSION: A sufficient decrease in tumor vascular parameters was observed at a dose chosen for additional phase II testing by conventional toxicity criteria. In addition, the day 2 vascular response measured using DCE-MRI seems to be a useful indicator of drug pharmacology, and additional research is needed to determine if it is a suitable marker for predicting clinical activity.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Oral
Adult
Aged
*Angiogenesis Inhibitors: AD, administration & dosage
Angiogenesis Inhibitors: PK, pharmacokinetics
Area Under Curve
Contrast Media: AD, administration & dosage
Drug Administration Schedule
Gadolinium DTPA: DU, diagnostic use
Humans
*Magnetic Resonance Imaging
Middle Aged
Neoplasms: BL, blood
*Neoplasms: DT, drug therapy
*Neovascularization, Pathologic: DT, drug therapy
Predictive Value of Tests
Research Support, Non-U.S. Gov't
Treatment Outcome

CAS REGISTRY NO.: 80529-93-7 (Gadolinium DTPA)

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Contrast Media)

L15 ANSWER 5 OF 9 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 4

ACCESSION NUMBER: 2005-22995 DRUGU T S

TITLE: Phase 2 study of the anti-angiogenesis agent AG-013736 in patients with poor prognosis acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

AUTHOR: Giles F J; **Steinfeldt H**; Bellamy W T; Bycott P; **Pithavala Y**; Reich S D; List A F

CORPORATE SOURCE: Univ.Texas-Syst.; Pfizer; Univ.Arizona; H.Lee-Moffitt-Cancer-Cent.

LOCATION: Houston, TX, San Diego, CA, Tucson, AZ; Tampa, FL, USA

SOURCE: Blood (104, No. 11, Pt. 1, 502a, 2004)
CODEN: BLOOAW ISSN: 0006-4971

AVAIL. OF DOC.: Leukemia, MD Anderson, Houston, TX, U.S.A.

LANGUAGE: English

DOCUMENT TYPE: Journal

ABSTRACT:

A Phase II study of p.o. AG-013736 in 12 elderly patients with poor prognosis acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) is reported. Side-effects included hypertension, mucositis, DVT, hoarseness, proteinuria and diarrhea. There were no responses. AG-013736 was well tolerated and further trials in combination with other treatment are considered warranted. (conference paper: 46th Annual Meeting of the American Society of Hematology,

San Diego, California, USA, December 4-7, 2004).

SECTION HEADING: T Therapeutics
S Adverse Effects

CLASSIF. CODE: 35 Adverse Reactions
51 Chemotherapy - clinical
64 Clinical Trials
73 Trial Preparations

CONTROLLED TERM:
[01] AG-013736 *TR; AG-013736 *AE; DR0068539 *RN; ACUTE *TR; MYELOID *TR; LEUKEMIA *TR; PRELEUKEMIA *TR; HYPERTENSION *AE; DIARRHEA *AE; MUCOSITIS *AE; PROTEINURIA *AE; HOARSENESS *AE; DEEP *AE; VEIN *AE; THROMBOSIS *AE; LYMPHOPROLIFERATIVE-DISEASE *TR; MARROW-DISEASE *TR; VASCULAR-DISEASE *AE; GASTROENTEROPATHY *AE; ORL-DISEASE *AE; CASES *FT; IN-VIVO *FT; PHASE-II *FT; CYTOSTATIC *FT; P.O. *FT; GERIATRICS *FT; ANGIOGENESIS-INHIBITORS *FT; CYTOSTATICS *FT; TRIAL-PREP. *FT; TYROSINE-KINASE-INHIBITORS *FT; CLIN.TRIAL *FT; TR *FT; AE *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L15 ANSWER 6 OF 9 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-32469 DRUGU P
TITLE: PK/PD modeling based on mouse xenograft tumor growth inhibition and the correlation to clinical exposure for VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736.
AUTHOR: Yamazaki S; Grazzini M L; Romero D; Amundson K; **Pithavala Y; Hu Lowe D D**
CORPORATE SOURCE: Pfizer
LOCATION: San Diego, CA, USA
SOURCE: Proc.Am.Assoc.Cancer Res. (96 Meet., 3003, 2005) ISSN: 0197-016X
AVAIL. OF DOC.: Pfizer Global Research and Development, San Diego, CA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

This pharmacokinetic (PK)/pharmacodynamic (PD) study was carried out in mice (bearing human colon carcinoma MV522 tumors) that were treated with various concentrations of p.o. or infused AG-013736. Based on clinical PK parameters and parameters from mouse PK/PD modeling, human PK/PD simulation was performed to investigate clinical dose projection. This line of research emphasizes the complexity of PK/PD modeling and the necessity of understanding and conducting the appropriate preclinical PK/PD studies in order to better aid clinical dose projection for the development of anti-cancer agents. (conference abstract: 96th Annual Meeting of the American Association for Cancer Research, Anaheim, California, USA, April 16-20, 2005).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 8 Pharmacokinetics
52 Chemotherapy - non-clinical
73 Trial Preparations

CONTROLLED TERM:
[01] AG-013736 *DM; AG-013736 *PH; COLON *OC; INTESTINE *OC;

GASTROENTEROPATHY *OC; CARCINOMA *OC; ANIMAL-NEOPLASM *OC; DR0068539 *RN; IN-VIVO *FT; MOUSE *FT; CYTOSTATIC *FT; P.O. *FT; INFUSION *FT; BLOOD-PLASMA *FT; CONC. *FT; HALF-LIFE *FT; BIOAVAILABILITY *FT; LAB.ANIMAL *FT; INJECTION *FT; PHARMACOKINETICS *FT; ANGIOGENESIS-INHIBITORS *FT; CYTOSTATICS *FT; TRIAL-PREP. *FT; TYROSINE-KINASE-INHIBITORS *FT; VEGF-ANTAGONISTS *FT; DM *FT; PH *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L15 ANSWER 7 OF 9 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-25224 DRUGU T P S
TITLE: Clinical and dynamic imaging results of the first phase I study of AG-013736, an oral anti-angiogenesis agent, in patients (pts) with advanced solid tumors.
AUTHOR: Rugo H S; Herbst R S; Liu G; Park J W; Kies M S; **Pithavala Y K**; McShane T M; **Steinfeldt H M**; Reich S D; Wilding G
CORPORATE SOURCE: Univ.California; Univ.Texas; Univ.Wisconsin; Pfizer
LOCATION: San Francisco; La Jolla, CA, Houston, TX, Madison, WI; Groton, CT, USA
SOURCE: J.Clin.Oncol. (22, No. 14, Suppl., 2503, 2004)
CODEN: JCONDN ISSN: 0732-183X
AVAIL. OF DOC.: University of California, San Francisco, California, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The pharmacokinetics, safety and efficacy of p.o. AG-013736 was investigated in a phase I study of 36 patients with advanced solid tumors. The maximum tolerated dose of AG-013736 was 5 mg, b.i.d., with dose-limiting toxicities of hypertension, hepatopathy, thrombosis, pancreatitis and stomatitis. Results demonstrate the promising anticancer activity of AG-013736. (conference abstract: 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, USA, June 5-8, 2004).

SECTION HEADING: T Therapeutics
P Pharmacology
S Adverse Effects

CLASSIF. CODE: 8 Pharmacokinetics
35 Adverse Reactions
51 Chemotherapy - clinical
64 Clinical Trials
73 Trial Preparations

CONTROLLED TERM:
[01] AG-013736 *TR; AG-013736 *AE; AG-013736 *DM; DR0068539 *RN; MAMMA *TR; MAMMA-DISEASE *TR; THYROID *TR; THYROID-DISEASE *TR; KIDNEY *TR; NEPHROPATHY *TR; LUNG *TR; PNEUMOPATHY *TR; CARCINOMA *TR; HYPERTENSION *AE; HEPATOPATHY *AE; THROMBOSIS *AE; PANCREATITIS *AE; STOMATITIS *AE; NEOPLASM *TR; VASCULAR-DISEASE *AE; PANCREOPATHY *AE; STOMATOLOGY *AE; IN-VIVO *FT; CASES *FT; PHASE-I *FT; P.O. *FT; DOSAGE *FT; CYTOSTATIC *FT; BLOOD-PLASMA *FT; CONC. *FT; HALF-LIFE *FT; BIOAVAILABILITY *FT; TRIAL-PREP. *FT; ANGIOGENESIS-INHIBITORS *FT; TYROSINE-KINASE-INHIBITORS *FT; CYTOSTATICS *FT; CLIN.TRIAL *FT; PHARMACOKINETICS *FT; TR *FT; AE *FT; DM *FT
FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

L15 ANSWER 8 OF 9 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-41475 DRUGU T P S
TITLE: A phase I study of the VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736 in patients with advanced solid tumors: Safety, pharmacokinetics and dceMRI.
AUTHOR: Herbst R; Rugo H; Liu G; Park J; Kies M; **Pithavala Y** ; McShane T; Evelhoch J; **Steinfeldt H**; Reich S; **Freddo J**; Wilding G
CORPORATE SOURCE: Univ.Texas-Syst.; Univ.California; Univ.Wisconsin; Pfizer
LOCATION: Houston, Tex., San Francisco; San Diego, Cal., Madison, Wis.; Groton, Conn., USA
SOURCE: Clin.Cancer Res. (9, No. 16, Pt. 2, 6265S, 2003) 3 Ref.
CODEN: CCREF ISSN: 1078-0432
AVAIL. OF DOC.: UT M.D. Anderson Cancer Center, Houston, TX, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

AG-013736 was given in escalating p.o. doses to 30 patients (pts) with solid tumors. The primary objective was to determine the maximum tolerated dose (MTD) and safety. Pharmacokinetics (PK), tumor vascular response by dceMRI, and efficacy were also evaluated. Tumor diagnoses were: breast (11), thyroid (5), renal cell (5), lung (4), and other (5). Toxicity included hypertension (HTN), seizure, hepatopathy, pancreatitis, apnea and stomatitis. 2 Durable partial responses were seen (in renal cell and adenoid cystic carcinomas) and stable disease lasting at least 4 mth (range: 4-13+ mth) was achieved in 5 pts of this heavily pretreated population. AG-013736 is concluded to be a highly active agent as manifested by clinical response and acute tumor vascular changes. (conference abstract: 2003 AACR-NCI-EORTC International Conference, Boston, Massachusetts, USA, 17-21 November, 2003).

SECTION HEADING: T Therapeutics
P Pharmacology
S Adverse Effects

CLASSIF. CODE: 8 Pharmacokinetics
35 Adverse Reactions
51 Chemotherapy - clinical
64 Clinical Trials
73 Trial Preparations

CONTROLLED TERM:
[01] AG-013736 *TR; AG-013736 *AE; AG-013736 *DM; DR0068539 *RN; MAMMA *TR; MAMMA-DISEASE *TR; CARCINOMA *TR; THYROID-DISEASE *TR; THYROID *TR; KIDNEY *TR; NEPHROPATHY *TR; LUNG *TR; PNEUMOPATHY *TR; HYPERTENSION *AE; EPILEPSY *AE; HEPATOPATHY *AE; PANCREATITIS *AE; APNEA *AE; STOMATITIS *AE; HEMOPTYSIS *AE; PROTEINURIA *AE; NEOPLASM *TR; VASCULAR-DISEASE *AE; ENCEPHALOPATHY *AE; PANCREOPATHY *AE; RESPIRATION-DISORDER *AE; STOMATOLOGY *AE; HEMORRHAGE *AE; TYROSINE-KINASE-INHIBITOR *FT; CYTOSTATIC *FT; P.O. *FT; CASES *FT; IN-VIVO *FT; CLIN.TRIAL *FT; DOSAGE *FT; BLOOD-PLASMA *FT; CONC. *FT; ABSORPTION *FT; CLEARANCE *FT; HALF-LIFE *FT; FASTING *FT; BIOAVAILABILITY *FT; ANGIOGENESIS-INHIBITOR *FT; PHASE-I *FT; TRIAL-PREP. *FT; CYTOSTATICS *FT; ANGIOGENESIS-INHIBITORS *FT; TYROSINE-KINASE-INHIBITORS *FT; PHARMACOKINETICS *FT; TR *FT; AE *FT; DM *FT

FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L15 ANSWER 9 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:147499 BIOSIS
DOCUMENT NUMBER: PREV200600148584
TITLE: A phase I/II study of AG-013736, an oral anti-angiogenesis agent, in combination with docetaxel in patients (pts) with metastatic breast cancer (MBC).
AUTHOR(S): Rugo, H. S. [Reprint Author]; Stopeck, A.; Badorf, A.; **Pithavala, Y. K.**; **Steinfeldt, H. M.**
CORPORATE SOURCE: Univ Calif San Francisco, San Francisco, CA 94143 USA
SOURCE: Breast Cancer Research and Treatment, (2005) Vol. 94, No. Suppl. 1, pp. S62.
Meeting Info.: 28th Annual San Antonio Breast Cancer Symposium. San Antonio, TX, USA. December 08 -11, 2005. San Antonio Canc Inst; Baylor Coll Med; an NCI-Designated Clin Canc Ctr; Canc Therapy & Res Ctr; Univ Texas San Antonio, Hlth Sci Ctr.
CODEN: BCTRD6. ISSN: 0167-6806.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Mar 2006
Last Updated on STN: 1 Mar 2006
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512
Urinary system - Pathology 15506
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
INDEX TERMS: Major Concepts
Pharmacology; Gynecology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences)
INDEX TERMS: Parts, Structures, & Systems of Organisms
breast: reproductive system
INDEX TERMS: Diseases
renal cell carcinoma: urologic disease, neoplastic disease
Carcinoma, Renal Cell (MeSH); Kidney Neoplasms (MeSH)
INDEX TERMS: Diseases
metastatic breast cancer: neoplastic disease, reproductive system disease/female
Breast Neoplasms (MeSH); Neoplasm Metastasis (MeSH)
INDEX TERMS: Chemicals & Biochemicals
docetaxel: antineoplastic-drug; BID; PDGF receptor tyrosine kinase; AG-013736: oral administration, antiangiogenesis agent, efficacy, phase II clinical trial, phase I clinical trial; VEGF receptor tyrosine kinase
INDEX TERMS: Methods & Equipment
xenotransplantation: laboratory techniques; chemotherapy: therapeutic and prophylactic techniques, clinical techniques

Searched by Barb O'Bryen, STIC 2-2518

ORGANISM:
Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): female
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER:
114977-28-5 (docetaxel)
101463-26-7 (PDGF receptor tyrosine kinase)
386705-49-3 (VEGF receptor tyrosine kinase)

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=> fil reg; d stat que l7
FILE 'REGISTRY' ENTERED AT 12:17:06 ON 10 AUG 2006
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STRUCTURE FILE UPDATES:    9 AUG 2006  HIGHEST RN 900096-56-2
DICTIONARY FILE UPDATES:   9 AUG 2006  HIGHEST RN 900096-56-2

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experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

L5              STR
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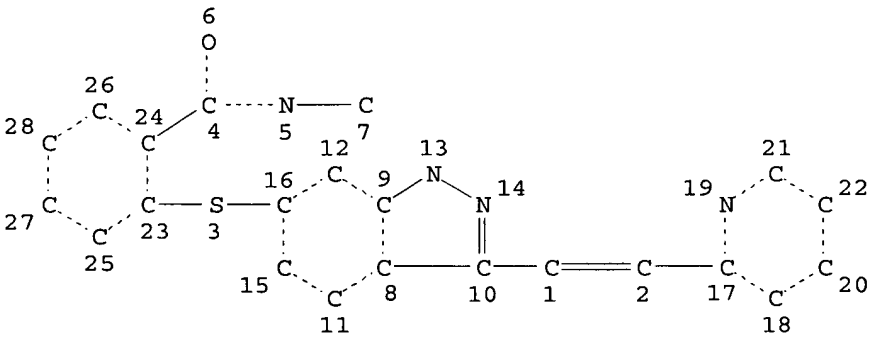

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  28

STEREO ATTRIBUTES: NONE
L7            3 SEA FILE=REGISTRY FAM FUL L5

100.0% PROCESSED      21 ITERATIONS                    3 ANSWERS
SEARCH TIME: 00.00.01


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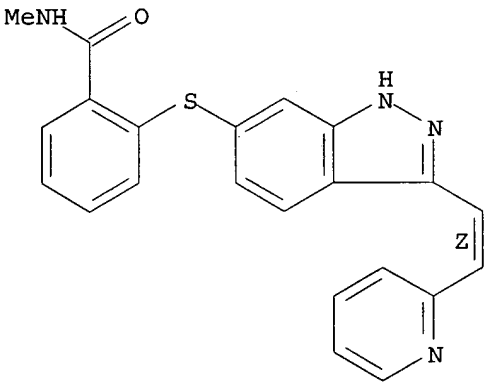
L7 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN 885126-40-9 REGISTRY
ED Entered STN: 22 May 2006
CN Benzamide, N-methyl-2-[[3-[(1Z)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H18 N4 O S
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPATFULL

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

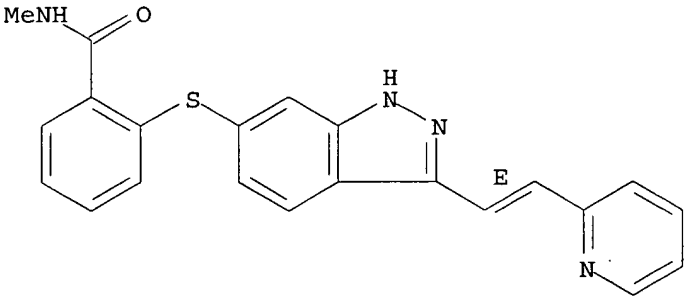
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L7 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN 771570-72-0 REGISTRY
ED Entered STN: 29 Oct 2004
CN Benzenepropanoic acid, β-[[(1,1-dimethylethoxy)carbonyl]amino]-α-hydroxy-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (αR,βS)-, mixt. with N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]benzamide (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C43 H53 N O14 . C22 H18 N4 O S
CI MXS
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 319460-85-0
CMF C22 H18 N4 O S

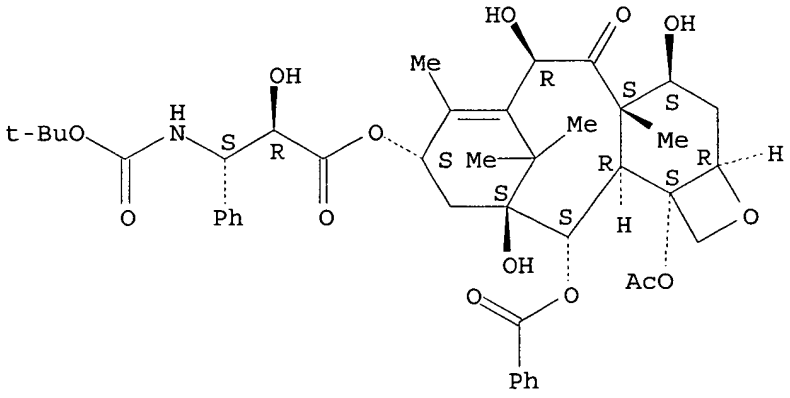
Double bond geometry as shown.



CM 2

CRN 114977-28-5
CMF C43 H53 N O14

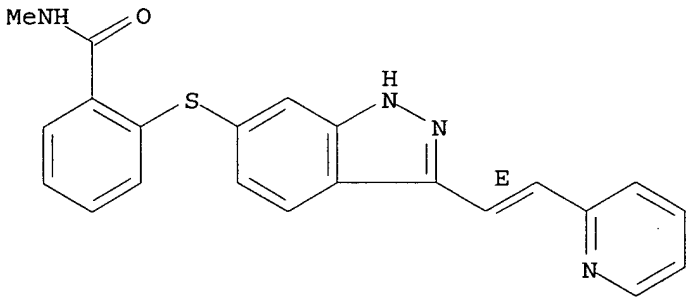
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L7 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN 319460-85-0 REGISTRY
ED Entered STN: 02 Feb 2001
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AG 013736
CN Axitinib
FS STEREOSEARCH
DR 790713-39-2
MF C22 H18 N4 O S
CI COM
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, CASREACT, IMSDRUGNEWS, IPA, PHAR, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

17 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
17 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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FILE 'CAPLUS' ENTERED AT 12:21:01 ON 10 AUG 2006
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FILE COVERS 1907 - 10 Aug 2006 VOL 145 ISS 7
FILE LAST UPDATED: 9 Aug 2006 (20060809/ED)

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They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L18 17 L7

=> s l18 not l1
L19 16 L18 NOT L1 previously printed w/ inventor search

=> fil ipa toxcenter prousddr phar adisin; s l7
FILE 'IPA' ENTERED AT 12:21:34 ON 10 AUG 2006

FILE 'TOXCENTER' ENTERED AT 12:21:34 ON 10 AUG 2006

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FILE 'PROUSDDR' ENTERED AT 12:21:34 ON 10 AUG 2006
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L20         19 L7

=> => fil wpix; d que l22
FILE 'WPIX' ENTERED AT 12:24:12 ON 10 AUG 2006
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FILE LAST UPDATED:          9 AUG 2006      <20060809/UP>
MOST RECENT DERWENT UPDATE:     200651        <200651/DW>
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http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

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    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE


L22          11 SEA FILE=WPIX ABB=ON  RA3G48/DCN OR 366778-0-0-0/DCRE OR
                AXITINIB/BI,ABEX OR AG013736/BI,ABEX OR AG 013736/BI,ABEX


=> dup rem l19,l20,l22
DUPLICATE IS NOT AVAILABLE IN 'PROUSDDR, PHAR, ADISINSIGHT'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'CAPLUS' ENTERED AT 12:24:22 ON 10 AUG 2006
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FILE 'PHAR' ENTERED AT 12:24:22 ON 10 AUG 2006
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FILE 'ADISINSIGHT' ENTERED AT 12:24:22 ON 10 AUG 2006

FILE 'WPIX' ENTERED AT 12:24:22 ON 10 AUG 2006

PROCESSING COMPLETED FOR L19
PROCESSING COMPLETED FOR L20
PROCESSING COMPLETED FOR L22
L23 22 DUP REM L19 L20 L22 (24 DUPLICATES REMOVED)
ANSWERS '1-16' FROM FILE CAPLUS
ANSWER '17' FROM FILE TOXCENTER
ANSWER '18' FROM FILE PROUSDDR
ANSWER '19' FROM FILE PHAR
ANSWER '20' FROM FILE ADISINSIGHT
ANSWERS '21-22' FROM FILE WPIX

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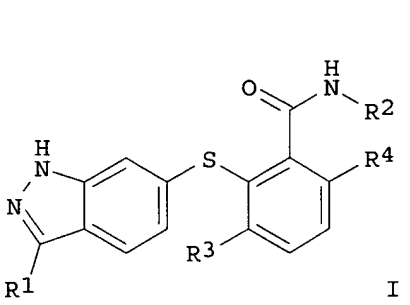
L23 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:436998 CAPLUS
DOCUMENT NUMBER: 144:468156
TITLE: Process for preparation of indazoles
INVENTOR(S): Babu, Srinivasan; Dagnino, Raymond, Jr.; Ouellette, Michael Allen; Shi, Bing; Tian, Qingping; Zook, Scott Edward
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006048745	A1	20060511	WO 2005-IB3300	20051021

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-624575P P 20041102
OTHER SOURCE(S): MARPAT 144:468156
ED Entered STN: 11 May 2006
GI



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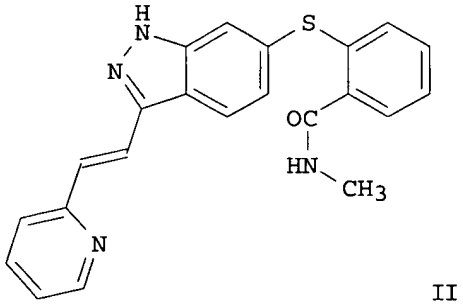


II

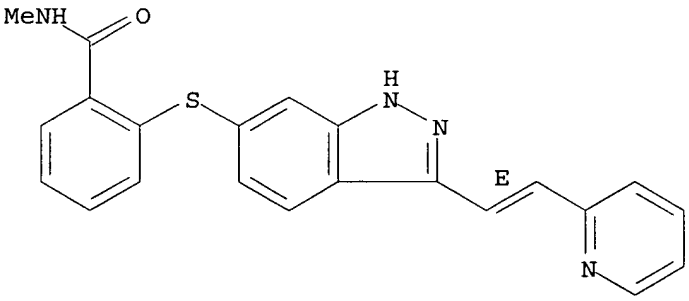
AB This invention relates to methods for preparing indazole derivs. I [wherein R1 = (un)substituted -CH=CH-R5 or -CH=N-R5; R2 = (un)substituted (cyclo)alkyl, (cyclo)alkoxy, aryloxy, (hetero)aryl, etc.; R3 and R4 = independently H, halo, or (un)substituted alkyl; R5 = (un)substituted (cyclo)alkyl, heterocycloalkyl, or (hetero)aryl], or pharmaceutically acceptable salts or solvates thereof. For example, intermediates 6-iodo-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole and 2-mercapto-N-methylbenzamide were prepared in multi-step syntheses comprising Heck vinylation, reduction, diazotization, and iodination reactions. The intermediates obtained in previous step were reacted in DMF at 80 °C for 4-16 h in the presence of palladium catalyst and cesium carbonate, followed by deprotecting the tetrahydropyanyl group in methanol in the presence of p-toluenesulfonic acid to give II in moderate yield. The title compds. are useful as modulators and/or inhibitors of protein kinases for the treatment of cancer or other diseases (no data).

IT **319460-85-0P**
RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation of indazoles)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

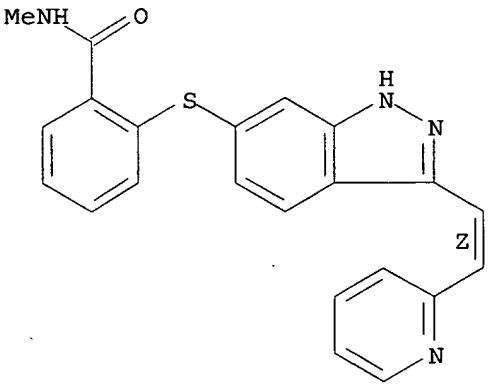


IT **885126-40-9P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of indazoles)

RN 885126-40-9 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1Z)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2006:268466 CAPLUS
DOCUMENT NUMBER: 144:324798
TITLE: Simultaneous use of sulfonamide-containing compound and angiogenesis inhibitor
INVENTOR(S): Owa, Takashi; Ozawa, Yoichi; Semba, Taro
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: PCT Int. Appl., 270 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006030941	A1	20060323	WO 2005-JP17228	20050913
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
WO 2006030947	A1	20060323	WO 2005-JP17238	20050913
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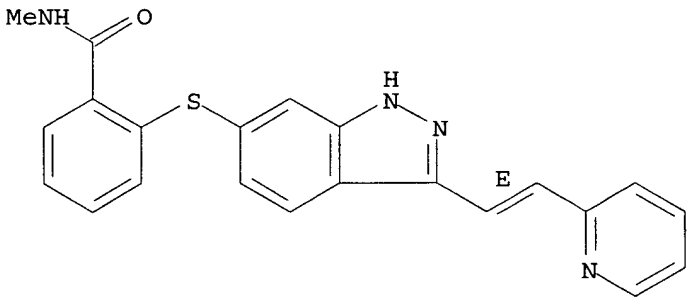
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,				

IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2006135486	A1	20060622	US 2005-226655	20050913
PRIORITY APPLN. INFO.:			US 2004-609452P	P 20040913
			JP 2005-54150	A 20050228
			JP 2005-54475	A 20050228

OTHER SOURCE(S): MARPAT 144:324798
ED Entered STN: 23 Mar 2006
AB A pharmaceutical composition comprising a sulfonamide-containing compound combined with an angiogenesis inhibitor.
IT **319460-85-0**, AG 013736
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulfonamide-containing compds. and angiogenesis inhibitors for combination chemotherapy of cancer)
RN 319460-85-0 CAPLUS
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2006:167588 CAPLUS
DOCUMENT NUMBER: 144:254148
TITLE: Aminopteridinones as anticancer agents, their preparation, pharmaceutical compositions, and use in therapy
INVENTOR(S): Munzert, Gerd; Steegmaier, Martin; Baum, Anke
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006018182	A1	20060223	WO 2005-EP8623	20050809
WO 2006018182	C1	20060608		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2006058311 A1 20060316 US 2005-189540 20050726

PRIORITY APPLN. INFO.: EP 2004-19361 A 20040814

EP 2004-19448 A 20040817

OTHER SOURCE(S): MARPAT 144:254148

ED Entered STN: 23 Feb 2006

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a group of aminopteridinones I, which are useful for the treatment of diseases which involve cell proliferation. In compds. I, R1 and R2 are independently selected from H and (un)substituted C1-6 alkyl, or R1 and R2 together form a 2- to 5-membered alkylene bridge, optionally containing 1 or 2 heteroatoms; R3 is (un)substituted C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl, C6-14 aryl, etc.; R4 is H, OH, CN, halo, (un)substituted amino, (un)substituted C1-6 alkyl, C1-5 alkoxy, etc.; L is (un)substituted C2-10 alkylene, (un)substituted C2-10 alkenylene, (un)substituted C6-14 arylene, etc.; R5 is (un)substituted morpholinyl, (un)substituted piperidinyl, (un)substituted piperazinyl, (un)substituted piperazinylcarbonyl, (un)substituted pyrrolidinyl, (un)substituted thiomorpholinyl, etc.; n is 0 or 1; and m is 1 or 2; including tautomers, stereoisomers, salts, solvates, polymorphs, and prodrugs thereof. The invention also relates to the preparation of I, pharmaceutical compns. comprising a compound I, at least one other therapeutic agent, optionally with one or more pharmaceutically acceptable excipients, as well as to the use of the compns. for the treatment of diseases which involve cell proliferation, migration or apoptosis of cancer cells, or angiogenesis. Esterification of (R)-2-aminobutyric acid and reductive condensation with cyclopentanone gave cyclopentylamine II, which underwent regioselective substitution of 2,4-dichloro-5-nitropyrimidine and reductive heterocyclization to form pteridinone III. N-Methylation of III followed by substitution with 4-amino-3-methoxybenzoic acid and amidation with 1-methyl-4-aminopiperidine resulted in the formation of aminopteridinone IV. A combination of suboptimal doses of irinotecan and compound IV shows an additive/synergistic effect in a human colon carcinoma model and is well tolerated. Meanwhile, compound IV acts at least additively with docetaxel in a human non-small cell lung carcinoma model and not antagonistically with gemcitabine in a human adenocarcinoma model.

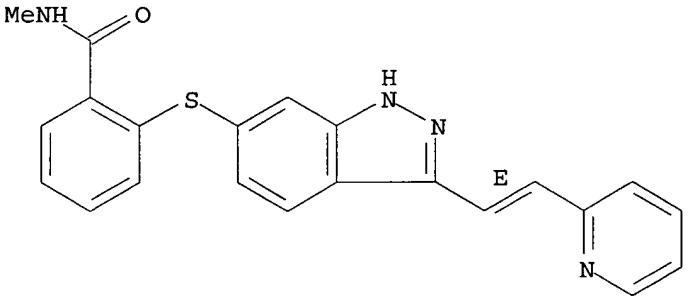
IT **319460-85-0**, AG 013736
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of aminopteridinones for use in combination therapy for treatment of cell proliferative diseases)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-

yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



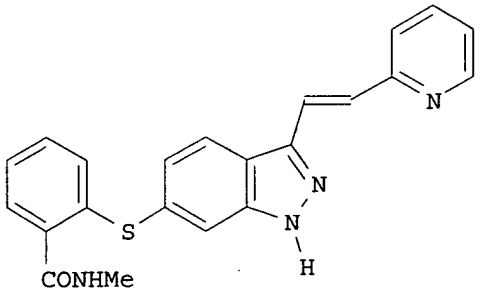
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2006:409892 CAPLUS
DOCUMENT NUMBER: 144:432800
TITLE: Preparation of indazole compounds as modulators and/or inhibitors of protein kinases
INVENTOR(S): Ewanicki, Brigitte Leigh; Flahive, Erik Jon; Kasparian, Annie Judith; Mitchell, Mark Bryan; Perry, Michael David; O'neill-Slawecki, Stacy Ann; Sach, Neal William; Saenz, James Edward; Shi, Bing; Stankovic, Nebojsa Slobodan; Srirangam, Jayaram Kasturi; Tian, Qingping; Yu, Shu
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 31 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006094881	A1	20060504	US 2005-264440	20051031
WO 2006048744	A1	20060511	WO 2005-IB3297	20051021

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-624635P P 20041102
US 2005-717071P P 20050914
OTHER SOURCE(S): CASREACT 144:432800; MARPAT 144:432800
ED Entered STN: 05 May 2006
GI



I

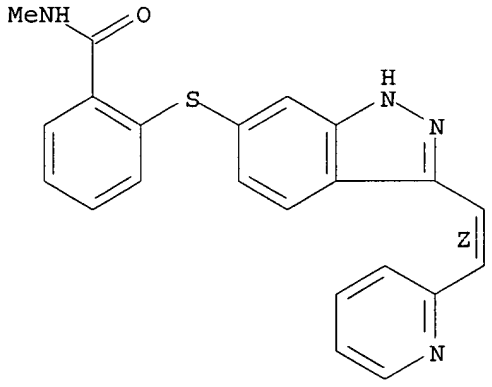
AB The present invention relates to methods for preparing indazole compds. which are useful as modulators and/or inhibitors of protein kinases. The present invention also relates to intermediate compds. useful in the preparation of the compds. E.g., I was prepared by reaction of 2-(3-iodo-1H-indazol-6-ylsulfanyl)-N-methylbenzamide and 2-vinylpyridine.

IT **885126-40-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of indazole compds. as modulators and/or inhibitors of protein kinases)

RN 885126-40-9 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1Z)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

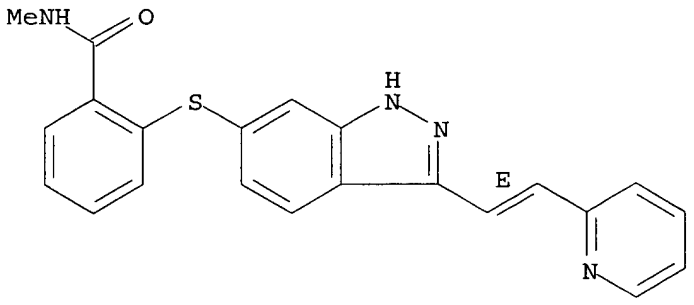


IT **319460-85-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of indazole compds. as modulators and/or inhibitors of protein kinases)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2006:409884 CAPLUS
DOCUMENT NUMBER: 144:439992
TITLE: Polymorphic forms of 6-[2-(methylcarbomoyl) phenyl sulfanyl]-3-E-[2-(pyridin-2-yl)ethenyl]indazole and pharmaceutical uses for hyperproliferative disorders
INVENTOR(S): Ye, Qiang; Hart, Ryan Marshal; Kania, Robert; Ouellette, Michael; Wu, Zhen Ping; Zook, Scott Edward
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 35 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

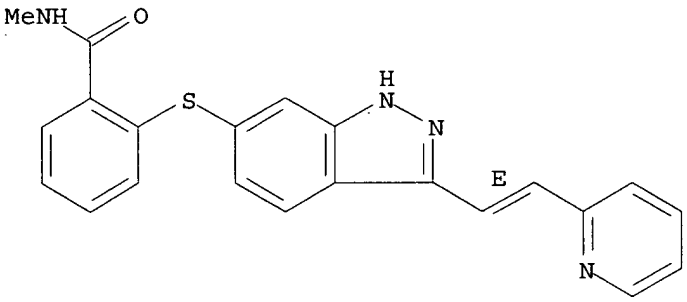
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006094763	A1	20060504	US 2005-264493	20051031
WO 2006048751	A1	20060511	WO 2005-IB3312	20051021

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-624665P P 20041102
ED Entered STN: 05 May 2006
AB The present invention relates to novel polymorphic forms of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridin-2-yl)ethenyl]indazole, and to processes for their preparation Such polymorphic forms may be a component of a pharmaceutical composition and may be used to treat a hyperproliferative disorder or a mammalian disease condition mediated by protein kinase activity.
IT **319460-85-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymorphic forms of 6-[2-(methylcarbomoyl) Ph sulfanyl]-3-E-[2-(pyridin-2-yl)ethenyl]indazole and pharmaceutical uses for hyperproliferative disorders)

RN 319460-85-0 CAPLUS
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

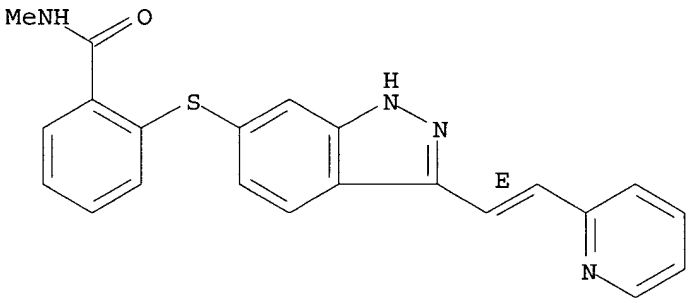
Double bond geometry as shown.



L23 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2006:189296 CAPLUS
DOCUMENT NUMBER: 144:324360
TITLE: Antiangiogenic Therapy Decreases Integrin Expression in Normalized Tumor Blood Vessels
AUTHOR(S): Yao, Virginia J.; Ozawa, Michael G.; Varner, Amanda S.; Kasman, Ian M.; Chanthery, Yvan H.; Pasqualini, Renata; Arap, Wadih; McDonald, Donald M.
CORPORATE SOURCE: Department of Anatomy, Cardiovascular Research Institute, Comprehensive Cancer Center, University of California, San Francisco, CA, USA
SOURCE: Cancer Research (2006), 66(5), 2639-2649
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Mar 2006
AB Tumor blood vessels normalized by antiangiogenic therapy may provide improved delivery of chemotherapeutic agents during a window of time but it is unknown how protein expression in tumor vascular endothelial cells changes. We evaluated the distribution of RGD-4C phage, which binds αv{szligbeta}3, αv{szligbeta}5, and α5{szligbeta}1 integrins on tumor blood vessels before and after antiangiogenic therapy. Unlike the control phage, fd-tet, RGD-4C phage homed to vascular endothelial cells in spontaneous tumors in RIP-Tag2 transgenic mice in a dose-dependent fashion. The distribution of phage was similar to αv{szligbeta}3 and α5{szligbeta}1 integrin expression. Blood vessels that survived treatment with AG-013736, a small mol. inhibitor of vascular endothelial growth factor and platelet-derived growth factor receptors, had only 4% as much binding of RGD-4C phage compared with vessels in untreated tumors. Cellular distribution of RGD-4C phage in surviving tumor vessels matched the α5{szligbeta}1 integrin expression. The reduction in integrin expression on tumor vessels after antiangiogenic therapy raises the possibility that integrin-targeted delivery of diagnostics or therapeutics may be compromised. Efficacious delivery of drugs may benefit from identification by in vivo phage display of targeting peptides that bind to tumor blood vessels normalized by antiangiogenic agents.
IT **319460-85-0**, AG 013736
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(antiangiogenic therapy effect on integrin in tumor blood vessels)
RN 319460-85-0 CAPLUS
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2006:394720 CAPLUS
DOCUMENT NUMBER: 145:39944
TITLE: Inhibition of phosphorylation of the colony-stimulating factor-1 receptor (c-Fms) tyrosine kinase in transfected cells by ABT-869 and other tyrosine kinase inhibitors
AUTHOR(S): Guo, Jun; Marcotte, Patrick A.; McCall, J. Owen; Dai, Yujia; Pease, Lori J.; Michaelides, Michael R.; Davidsen, Steven K.; Glaser, Keith B.
CORPORATE SOURCE: Cancer Discovery Research (R47J), Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA
SOURCE: Molecular Cancer Therapeutics (2006), 5(4), 1007-1013 CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 May 2006
AB The properties of several multitargeted receptor tyrosine kinase inhibitors were studied for their inhibition of colony-stimulating factor-1 receptor (CSF-1R) signaling. A structurally novel, multitargeted tyrosine kinase inhibitor (ABT-869), imatinib (STI571), and 4 compds. currently in clin. development (AG013736, BAY 43-9006, CHIR258, and SU11248) were tested for inhibition of CSF-1R signaling in both the enzymic and cellular assays. ABT-869 showed potent CSF-1R inhibition in both the enzyme and cell-based assays (IC50s < 20 nmol/L). In contrast to a previous report, we have found that imatinib has activity against human CSF-1R in both assays at submicromolar concns. In enzyme assays, we have found that the inhibition of CSF-1R by both ABT-869 and imatinib are competitive with ATP, with Ki values of 3 and 120 nmol/L, resp. SU11248 is a potent inhibitor of CSF-1R in the enzyme assay (IC50 = 7 nmol/L) and inhibits receptor phosphorylation in the cellular assay (IC50 = 61 nmol/L). AG013736 was also a potent inhibitor of CSF-1R in both assays (enzyme, IC50 = 16 nmol/L; cellular, IC50 = 21 nmol/L), whereas BAY 43-9006 is less potent in the enzyme assay (IC50 = 107 nmol/L) than in the

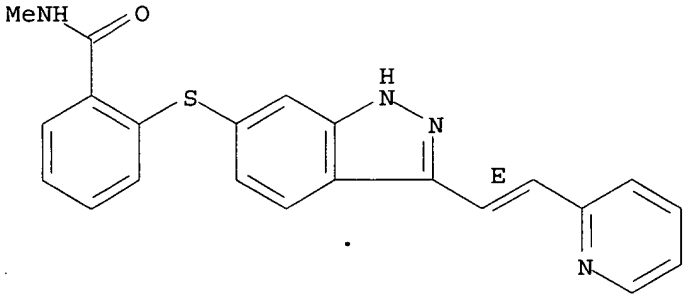
cellular system (IC50 = 20 nmol/L). In contrast, we found that CHIR258 had less activity in the cellular assay (IC50 = 535 nmol/L) relative to its enzymic potency (IC50 = 26 nmol/L). These results show the use of a cell-based assay to confirm the inhibitory activity of lead compds. and drug candidates, such as ABT-869, against the CSF-1R protein in situ.

IT **319460-85-0**, AG 013736
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AG 013736; inhibition of phosphorylation of c-Fms receptor tyrosine kinase in cells by ABT-869)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 2005:1294044 CAPLUS
DOCUMENT NUMBER: 144:17160
TITLE: Method using camptothecin compounds, pyrimidine derivatives, and antitumor agents for treating abnormal cell growth
INVENTOR(S): Denis, Louis J.; Compton, Linda D.
PATENT ASSIGNEE(S): Pfizer Inc, USA
SOURCE: U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005272755	A1	20051208	US 2005-145097	20050603
WO 2005117980	A1	20051215	WO 2005-IB1527	20050523

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-577268P P 20040604

ED Entered STN: 09 Dec 2005

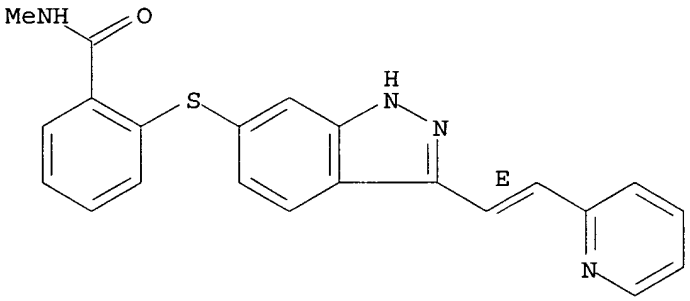
AB The invention discloses a method for treating abnormal cell growth in a subject, comprising administering to the subject (a) a compound selected from a camptothecin, a camptothecin derivative, or a pharmaceutically acceptable salt, solvate or prodrug thereof; (b) a pyrimidine derivative or a pharmaceutically acceptable salt, solvate or prodrug thereof; and (c) an antitumor agent selected from antiproliferative agents, kinase inhibitors, angiogenesis inhibitors, growth factor inhibitors, COX-1 inhibitors, COX-2 inhibitors, mitotic inhibitors, alkylating agents, antimetabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biol. response modifiers, antibodies, cytotoxics, antihormones, antiandrogens and combinations thereof.

IT **319460-85-0**, AG 013736
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AG 013736; camptothecin compds., pyrimidine derivs., and antitumor agents for treatment of abnormal cell growth)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 2005:140815 CAPLUS

DOCUMENT NUMBER: 142:212410

TITLE: Indazole compounds and pharmaceutical compositions for inhibiting protein kinases, and their therapeutic use

INVENTOR(S): Bender, Steven; Skalitzky, Donald J.; Hu-Lowe, Dana

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 326,037.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

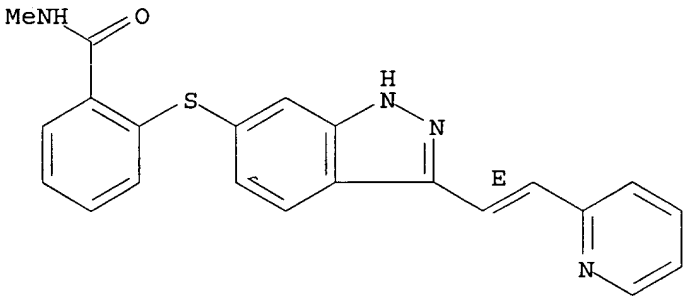
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005038097	A1	20050217	US 2003-639890	20030812

EP 1614683	A1	20060111	EP 2005-15902		20000630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
US 6531491	B1	20030311	US 2001-983786		20011025
US 6534524	B1	20030318	US 2001-983783		20011025
US 2004171634	A1	20040902	US 2003-326755		20030213
US 6884890	B2	20050426			
US 2004220248	A1	20041104	US 2003-326037		20030215
US 6891044	B2	20050510			
US 2005124662	A1	20050609	US 2004-992146		20041118
PRIORITY APPLN. INFO.:			US 1999-142130P	P	19990702
			US 2000-609335	B3	20000630
			US 2001-983783	A3	20011025
			US 2003-326037	A2	20030215
			EP 2000-943375	A3	20000630
			US 2001-983786	A3	20011025

OTHER SOURCE(S): MARPAT 142:212410
ED Entered STN: 18 Feb 2005
AB Indazole compds. that modulate and/or inhibit the activity of certain protein kinases are described. These compds. and pharmaceutical compns. containing them are capable of mediating tyrosine kinase signal transduction and thereby modulate and/or inhibit unwanted cell proliferation. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compns. containing such compds., and to methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis, by administering effective amts. of such compds.
IT **319460-85-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indazole compds. and pharmaceutical compns. for inhibiting protein kinases, and therapeutic use)
RN 319460-85-0 CAPLUS
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

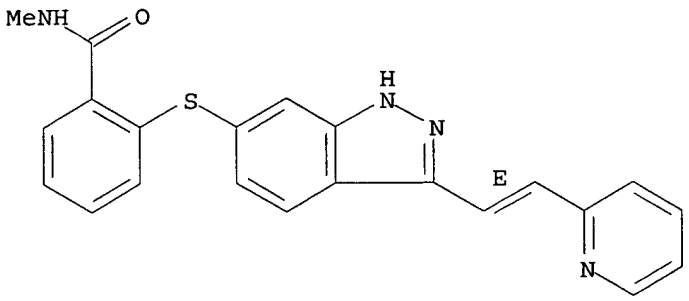
Double bond geometry as shown.



L23 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2005:1038009 CAPLUS
DOCUMENT NUMBER: 144:80723
TITLE: Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results
AUTHOR(S): Rugo, Hope S.; Herbst, Roy S.; Liu, Glenn; Park, John

W.; Kies, Merrill S.; Steinfeldt, Heidi M.; Pithavala, Yazdi K.; Reich, Steven D.; Freddo, James L.; Wilding, George
CORPORATE SOURCE: San Francisco Comprehensive Cancer Center, University of California, San Francisco, USA
SOURCE: Journal of Clinical Oncology (2005), 23(24), 5474-5483
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: American Society of Clinical Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 28 Sep 2005
AB Purpose: We studied the safety, clin. activity, and pharmacokinetics (PK) of AG-013736, an oral receptor tyrosine kinase inhibitor of vascular endothelial cell growth factor, platelet-derived growth factor, and c-Kit, in patients with advanced cancer. Patients and Methods: Patients received fixed doses of AG-013736 orally in 28-day cycles. In the first cohort, patients initially received two single test doses of AG-013736 (10 and 30 mg); subsequent dosing was determined by individual PK parameters. Doses in subsequent cohorts were assigned by using a traditional dose-escalation/de-escalation rule based on observed toxicities in the current and previous cohorts. PK anal. included evaluation of the effect of food and antacid. Results: Thirty-six patients received AG-013736 at doses ranging from 5 to 30 mg by mouth twice daily. The dose-limiting toxicities observed included hypertension, hemoptysis, and stomatitis and were seen primarily at the higher dose levels. The observed hypertension was manageable with medication. Stomatitis was generally tolerable and managed by dose reduction or drug holidays. AG-013736 was absorbed rapidly, with peak plasma concns. observed within 2 to 6 h after dosing. The maximum-tolerated dose and recommended phase II dose of AG-013736 is 5 mg, twice daily, administered in the fasted state. No significant drug interaction with antacid was seen. There were three confirmed partial responses and other evidence of clin. activity. Conclusion: In this study, we have demonstrated clin. activity and safety of AG-013736 in patients with advanced solid tumors and identified the dose for phase II testing. The unique phase I study design allowed early identification of important absorption and metabolic issues critical to phase II testing of this agent.
IT **319460-85-0**, AG 013736
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase I trial showed MTD, RD of oral antiangiogenic agent AG-013736 was 5mg BID and was effective, safe with high Cmax, AUC and low Tmax, T1/2 despite of manageable DLTs in patient with advanced solid tumors)
RN 319460-85-0 CAPLUS
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

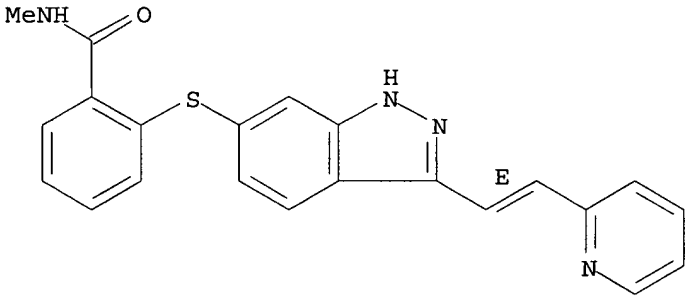
L23 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 2005:1038008 CAPLUS
DOCUMENT NUMBER: 144:80496
TITLE: Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: results from a phase I study
AUTHOR(S): Liu, Glenn; Rugo, Hope S.; Wilding, George; McShane, Teresa M.; Evelhoch, Jeffrey L.; Ng, Chaan; Jackson, Edward; Kelcz, Frederick; Yeh, Benjamin M.; Lee, Fred T., Jr.; Charnsangavej, Chusilp; Park, John W.; Ashton, Edward A.; Steinfeldt, Heidi M.; Pithavala, Yazdi K.; Reich, Steven D.; Herbst, Roy S.
CORPORATE SOURCE: Comprehensive Cancer Center, University of Wisconsin, Madison, WI, USA
SOURCE: Journal of Clinical Oncology (2005), 23(24), 5464-5473
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: American Society of Clinical Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 28 Sep 2005
AB Purpose: Identifying suitable markers of biol. activity is important when assessing novel compds. such as angiogenesis inhibitors to optimize the dose and schedule of therapy. Here we present the pharmacodynamic response to acute dosing of AG-013736 measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Patients and Methods: Thirty-six patients with advanced solid tumors were treated with various doses of AG-013736. In addition to standard measures of objective disease response and pharmacokinetic anal., DCE-MRI scans were acquired at baseline and repeated at cycle 1-day 2 after the scheduled morning dose of the AG-013736 in 26 patients. Indicators of a vascular response, such as the volume transfer constant (Ktrans) and initial area under the curve (IAUC), were calculated to assess the effect of treatment on tumor vascular function. Results: Evaluable vascular response data were obtained in 17 (65%) of 26 patients. A linear correlation was found in which the percentage change from baseline to day 2 in Ktrans and IAUC was inversely proportional to AG-013736 exposure. Using a conservative a priori assumption that a ≥50% decrease in Ktrans was indicative of an objective vascular response, a 50% decrease in Ktrans was achieved and corresponded to a plasma AUC0-24 of > 200 ng · h/mL. Conclusion: A sufficient decrease in tumor vascular parameters was observed at a dose chosen for addnl. phase II testing by conventional toxicity criteria. In addition, the

day 2 vascular response measured using DCE-MRI seems to be a useful indicator of drug pharmacol., and addnl. research is needed to determine if it is a suitable marker for predicting clin. activity.

IT **319460-85-0**, AG 013736
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiogenic inhibitor AG-013736 dose measured by DCE-MRI was effective with decreased tumor vascular response parameters Ktrans, IAUC and increased pharmacokinetic parameters Cmax, AUC in patient with advanced solid tumor)

RN 319460-85-0 CAPLUS
CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 2004:1059176 CAPLUS
DOCUMENT NUMBER: 142:32986
TITLE: Use of a c-abl-, PDGFR-, or c-kit-tyrosine kinase inhibitor for the treatment of diabetes
INVENTOR(S): Hagerkvist, Robert Per; Welsh, Nils Richard
PATENT ASSIGNEE(S): Swed.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004105763	A2	20041209	WO 2004-EP5679	20040526
WO 2004105763	A3	20050602		

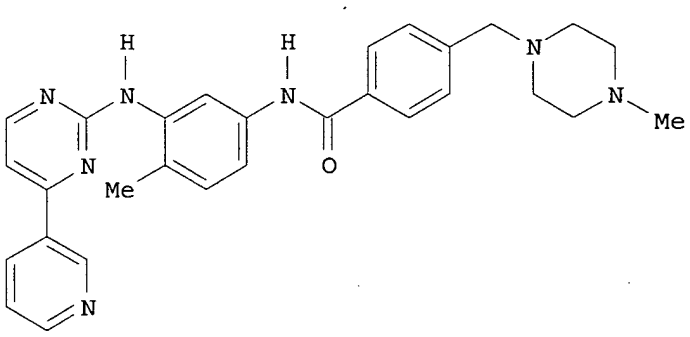
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,

SN, TD, TG

AU 2004243491	A1	20041209	AU 2004-243491		20040526
CA 2526594	AA	20041209	CA 2004-2526594		20040526
EP 1631291	A2	20060308	EP 2004-739375		20040526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR					
BR 2004010704	A	20060613	BR 2004-10704		20040526
CN 1794995	A	20060628	CN 2004-80014278		20040526
NO 2005006188	A	20051223	NO 2005-6188		20051223
PRIORITY APPLN. INFO.:			GB 2003-12086	A	20030527
			GB 2004-2682	A	20040206
			WO 2004-EP5679	W	20040526

ED Entered STN: 10 Dec 2004

GI



I

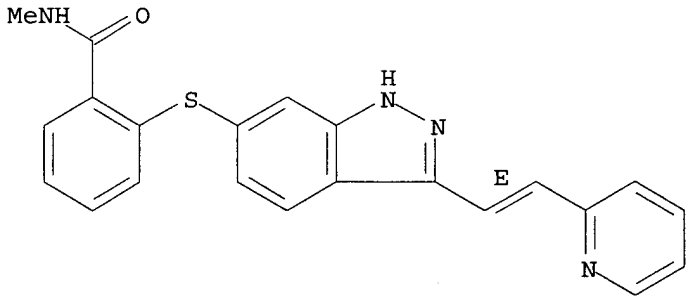
AB The invention discloses the use of a c-Abl-,PDGFR-, or c-kit-tyrosine kinase inhibitor, e.g. I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of diabetes, including type I or type II diabetes.

IT **319460-85-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(c-abl-, PDGFR-, or c-kit-tyrosine kinase inhibitor for treatment of diabetes)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 2004:965067 CAPLUS
DOCUMENT NUMBER: 141:406039
TITLE: Combinations for the treatment of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis
INVENTOR(S): Hilberg, Frank; Solca, Flavio; Stefanic, Martin Friedrich; Baum, Anke; Munzert, Gerd; Van Meel, Jacobus C. A.
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004096224	A2	20041111	WO 2004-EP4363		20040424
WO 2004096224	A3	20041216			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1473043	A1	20041103	EP 2003-9587		20030429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
AU 2004233576	A1	20041111	AU 2004-233576		20040424
CA 2523868	AA	20041111	CA 2004-2523868		20040424
EP 1622619	A2	20060208	EP 2004-729366		20040424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK					
BR 2004009919	A	20060425	BR 2004-9919		20040424
NO 2005005605	A	20051128	NO 2005-5605		20051128
PRIORITY APPLN. INFO.:			EP 2003-9587	A	20030429
			EP 2004-508	A	20040113
			EP 2004-1171	A	20040121
			WO 2004-EP4363	W	20040424

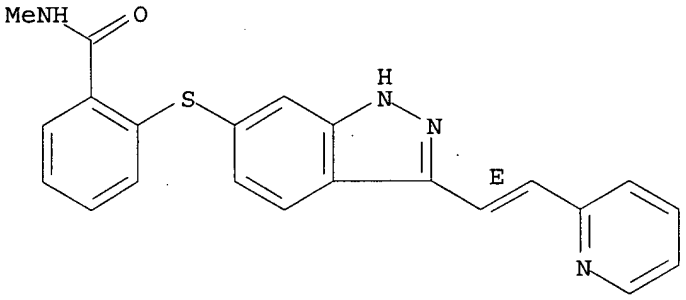
ED Entered STN: 12 Nov 2004
AB The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said diseases, comprising co-administration of effective amts. of specific active compds. and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compds. and/or radiotherapy for the manufacture of corresponding pharmaceutical combination prepns. The pharmaceutical combination can include selected protein tyrosine kinase receptor antagonists and further chemotherapeutic or naturally occurring semisynthetic or synthetic agents.
IT **319460-85-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(drug combinations for diseases involving cell proliferation and migration or apoptosis or angiogenesis including protein tyrosine kinase receptor antagonists and radiotherapy)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L23 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 14

ACCESSION NUMBER: 2004:905786 CAPLUS

DOCUMENT NUMBER: 141:391040

TITLE: Crystal structure of human VEGFR2 kinase domain-ligand complexes and use of the atomic coordinates in drug discovery

INVENTOR(S): Bender, Steven Lee; Kania, Robert Steven; McTigue, Michele Ann; Palmer, Cynthia Louise; Pinko, Chris; Wickersham, John

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: PCT Int. Appl., 332 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092217	A1	20041028	WO 2004-IB1251	20040405
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1618133	A1	20060125	EP 2004-725768	20040405
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
US 2005197492	A1	20050908	US 2004-824982	20040415
PRIORITY APPLN. INFO.:			US 2003-463957P	P 20030417

WO 2004-IB1251 W 20040405

ED Entered STN: 29 Oct 2004

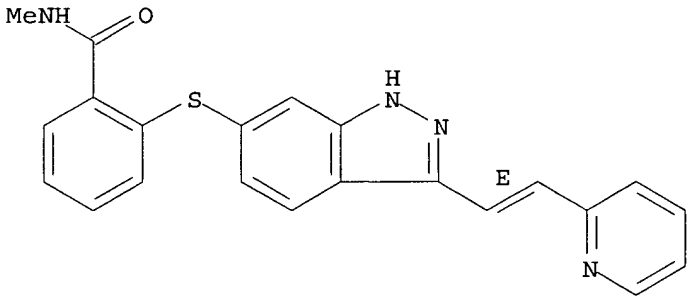
AB Polypeptides containing the kinase domain of human vascular endothelial growth factor receptor tyrosine kinase (VEGFR) are described. Also described are crystal structures of these polypeptides, including the crystal structures of VEGFR2 kinase domain-ligand complexes. The atomic coordinates derived from the crystal structures provide a three-dimensional description of the ligand-binding pocket of the kinase domain useful in drug discovery and design for the identification and design of modulators of kinase activity.

IT **319460-85-0DP**, complexes with VEGFR2 kinase domain
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(crystal structure of human VEGFR2 kinase domain-ligand complexes and use of atomic coordinates in drug discovery)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 16

ACCESSION NUMBER: 2004:618309 CAPLUS

DOCUMENT NUMBER: 142:86940

TITLE: Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts

AUTHOR(S): Inai, Tetsuichiro; Mancuso, Michael; Hashizume, Hiroya; Baffert, Fabienne; Haskell, Amy; Baluk, Peter; Hu-Lowe, Dana D.; Shalinsky, David R.; Thurston, Gavin; Yancopoulos, George D.; McDonald, Donald M.

CORPORATE SOURCE: Cardiovascular Research Institute, Comprehensive Cancer Center, and Department of Anatomy, University of California, San Francisco, CA, USA

SOURCE: American Journal of Pathology (2004), 165(1), 35-52
CODEN: AJPAA4; ISSN: 0002-9440

PUBLISHER: American Society for Investigative Pathology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 03 Aug 2004

AB Angiogenesis inhibitors are receiving increased attention as cancer therapeutics, but little is known of the cellular effects of these inhibitors on tumor vessels. We sought to determine whether two agents,

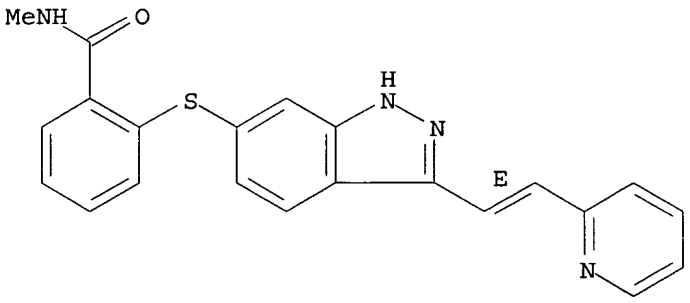
AG013736 and VEGF-Trap, that inhibit vascular endothelial growth factor (VEGF) signaling, merely stop angiogenesis or cause regression of existing tumor vessels. Here, we report that treatment with these inhibitors caused robust and early changes in endothelial cells, pericytes, and basement membrane of vessels in spontaneous islet-cell tumors of RIP-Tag2 transgenic mice and in s.c. implanted Lewis lung carcinomas. Strikingly, within 24 h, endothelial fenestrations in RIP-Tag2 tumors disappeared; vascular sprouting was suppressed, and patency and blood flow ceased in some vessels. By 7 days, vascular d. decreased more than 70%, and VEGFR-2 and VEGFR-3 expression was reduced in surviving endothelial cells. Vessels in Lewis lung tumors, which lacked endothelial fenestrations, showed less regression. In both tumors, pericytes did not degenerate to the same extent as endothelial cells, and those on surviving tumor vessels acquired a more normal phenotype. Vascular basement membrane persisted after endothelial cells degenerated, providing a ghost-like record of pretreatment vessel number and location and a potential scaffold for vessel regrowth. The potent anti-vascular action observed is evidence that VEGF signaling inhibitors do more than stop angiogenesis. Early loss of endothelial fenestrations in RIP-Tag2 tumors is a clue that vessel phenotype may be predictive of exceptional sensitivity to these inhibitors.

IT **319460-85-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AG013736 inhibited vascular endothelial growth factor signaling in cancer and caused loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts in mouse)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 17

ACCESSION NUMBER: 2001:31473 CAPLUS

DOCUMENT NUMBER: 134:100864

TITLE: Indazole compounds and pharmaceutical compositions for inhibiting protein kinases, and methods for their use

INVENTOR(S): Kania, Robert Steven; Bender, Steven Lee; Borchardt, Allen J.; Braganza, John F.; Cripps, Stephan James; Hua, Ye; Johnson, Michael David; Johnson, Theodore Otto, Jr.; Luu, Hiep The; Palmer, Cynthia Louise; Reich, Siegfried Heinz; Tempczyk-russell, Anna Maria; Teng, Min; Thomas, Christine; Varney, Michael David;

Wallace, Michael Brennan
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 439 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001002369	A2	20010111	WO 2000-US18263	20000630
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2383630	AA	20010111	CA 2000-2383630	20000630
BR 2000012352	A	20020514	BR 2000-12352	20000630
EP 1218348	A2	20020703	EP 2000-943375	20000630
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JP 2003503481	T2	20030128	JP 2001-507809	20000630
NZ 516676	A	20030926	NZ 2000-516676	20000630
CN 1495171	A	20040512	CN 2003-154858	20000630
AU 777701	B2	20041028	AU 2000-57852	20000630
EP 1614683	A1	20060111	EP 2005-15902	20000630
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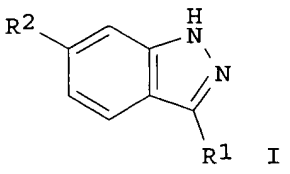
NO 2001005797	A	20020301	NO 2001-5797	20011128
ZA 2001010061	A	20030206	ZA 2001-10061	20011206
BG 106380	A	20020930	BG 2002-106380	20020201
HK 1048813	A1	20041210	HK 2003-101000	20030212
US 2004171634	A1	20040902	US 2003-326755	20030213
US 6884890	B2	20050426		

PRIORITY APPLN. INFO.:	US 1999-142130P	P 19990702
	EP 2000-943375	A3 20000630
	US 2000-609335	B3 20000630
	WO 2000-US18263	W 20000630
	US 2001-983786	A3 20011025

OTHER SOURCE(S): MARPAT 134:100864
ED Entered STN: 12 Jan 2001
GI



I

AB Indazole compds. I [R1 = substituted or unsubstituted aryl or heteroaryl, R3CH:CH, R3N:CH; R2 = substituted or unsubstituted aryl, heteroaryl, Y-X; R3 = substituted or unsubstituted alkyl alkenyl, cycloalkyl,

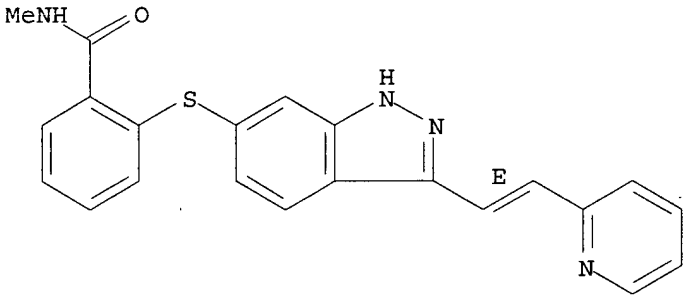
heterocycloalkyl, aryl, heteroaryl; Y = O, S, C(:CH2), CO, SO, SO2, alkylidene, NH, N(C1-C8 alkyl); X = substituted or unsubstituted aryl, heteroaryl, NH(alkyl), NH(cycloalkyl), NH(heterocycloalkyl), NH(aryl), NH(heteroaryl), NH(alkoxy), NH(dialkylamide)] and their pharmaceutically acceptable prodrugs, active metabolites, and salts are disclosed. The compds. modulate and/or inhibit the activity of certain protein kinases. In particular, I and pharmaceutical compns. containing them are capable of mediating tyrosine kinase signal transduction, and thereby modulate and/or inhibit unwanted cell proliferation. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compns. containing such compds., and to methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis, by administering effective amts. of such compds. E.g., I [R1 = (E)-3,4-(MeO)2C6H3CH:CH; R2 = 4-HO-3-MeOC6H3] (II) was prepared from 6-aminoindazole by diazotization and substitution with iodide, protection of the indazole nitrogen with 2,4,6-Me3C6H2SO2Cl, coupling of the regioisomeric mixture with 4-(methoxymethoxy)-3-methoxybenzeneboronic acid in the presence of dichlorobis(triphenylphosphine)palladium, and deprotection of the indazole moiety and iodination at the 3-position of the indazole. Treatment of the 3-indazolyl iodide with sec-butyllithium, phenyllithium, and DMF, regioselective protection of the indazole with 2,4,6-Me3C6H2SO2Cl, olefination with 3,4-dimethoxybenzyltriphenylphosphonium bromide, deprotection of the indazole, deprotection of the methoxymethyl group, and equilibration of the double bond with iodine gave II. Biol. data on protein kinase inhibition, cell proliferation inhibition, neovascularization inhibition, and i.p. and oral bioavailability, are given.

IT **319460-85-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aryl-substituted indazole derivs. as modulators and inhibitors of protein kinases in the treatment of tumor growth, cellular proliferation, and angiogenesis)

RN 319460-85-0 CAPLUS

CN Benzamide, N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



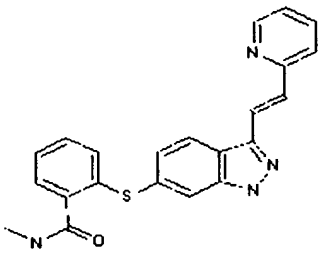
L23 ANSWER 17 OF 22 TOXCENTER COPYRIGHT 2006 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 2004:238078 TOXCENTER

COPYRIGHT: Copyright 2006 ACS
DOCUMENT NUMBER: CA141203377720
TITLE: Pharmaceutical dosage forms comprising AG 013736
AUTHOR(S): Freddo, James Lawrence; Hu-Lowe, Dana; Pithavala, Yazdi Kersi; Steinfeldt, Heidi Marie
CORPORATE SOURCE: ASSIGNEE: Pfizer Inc.
PATENT INFORMATION: WO 2004087152 A1 14 Oct 2004
SOURCE: (2004) PCT Int. Appl., 35 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2004:857398
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Oct 2004
Last Updated on STN: 30 May 2006

ABSTRACT:
The invention provides pharmaceutical dosage forms of AG 013736 or salts, solvates or prodrugs. The invention further provides methods of treating abnormal cell growth, such as cancers, by administering the dosage forms to a mammal. A high-dose combination therapy of AG 013736 ad docetaxel generates greater delay of primary tumor growth and metastasis than either monotherapy alone.
CLASSIFICATION CODE: 63-6
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
AG0 13736 pharmaceutical antitumor
REGISTRY NUMBER: 80449-01-0 (Topoisomerase)
114977-28-5 (Docetaxel)
REGISTRY NUMBER: **319460-85-0**; **771570-72-0**; 108334-68-5

L23 ANSWER 18 OF 22 PROUSDDR COPYRIGHT 2006 PROUS SCIENCE on STN
ACCESSION NUMBER: 2003:98 PROUSDDR
DOCUMENT NUMBER: 318296
CHEMICAL NAME: N-Methyl-2-(3-(2-(2-pyridyl)vinyl)-1H-indazol-6-ylsulfanyl)benzamide
DRUG NAME: AG-013736
AG-13736
GENERIC NAME: Axitinib (Prop INN, USAN)
CAS REGISTRY NUMBER: **319460-85-0**
MOLECULAR FORMULA: C22 H18 N4 O S
STATUS: Actively Investigated
HIGHEST DEV. PHASE: PHASE II
ORIGINATOR: Pfizer
CLASSIFICATION CODE: Breast Cancer Therapy; Pancreatic Cancer Therapy; Renal Cancer Therapy
ACTION MECHANISM: Angiogenesis Inhibitors
OTHER SOURCE: SYNTHLINE 2004000274
ENTRY DATE: Entered STN: 9 May 2004
Last Updated on STN: 4 Aug 2006

STRUCTURE:



PROUS REFERENCES:
RefID: 740156 (Text Available)
Drug Data Report, Vol. 25, No. 7, pp 657, 2003

REFERENCE TEXT: RefID: 740156
ACTION - Potent, selective and orally active inhibitor of VEGFR/PDGFR (vascular endothelial growth factor receptor/platelet-derived growth factor receptor) tyrosine kinases, currently in phase I clinical trials in patients with advanced solid tumors. It inhibited VEGFR1 and VEGFR2 tyrosine kinases (Ki = 2.6 and 3.7 nM, respectively), VEGF-induced phosphorylation of VEGFR2 (IC50 = 7.2 nM) and MAPK in human umbilical vein endothelial cells (HUVEC). It also inhibited VEGFR2 and PDGFRbeta phosphorylation in rat retina and human tumor xenografts following single oral doses, as well as VEGF-induced skin vascular leakage in mice when administered as single oral doses of 0.3-10 mg/kg. Compound exhibited broad antitumor activity in preclinical xenograft models of human colon carcinoma MV522 (3-100 mg/kg b.i.d.), murine Lewis lung carcinoma (ED50 = 1.2 mg/kg b.i.d.), breast carcinoma BT-474 and melanoma, inhibiting tumor growth, angiogenesis and metastasis.

PATENT REFERENCES:

TITLE: Indazole compounds and pharmaceutical compositions for inhibiting protein kinases, and methods for their use
INVENTOR(S): Luu, H.T.; Varney, M.D.; Palmer, C.L.; Reich, S.H.; Teng, M.; Bender, S.L.; Cripps, S.J.; Johnson, M.D.; Thomas, C.; Wallace, M.B.; Johnson, T.O. Jr.; Kania, R.S.; Borchardt, A.J.; Braganza, J.F.; Hua, Y.; Tempczyk-Russell, A.M.
PATENT ASSIGNEE(S): Agouron
PATENT INFORMATION: EP 1614683 20060111
JP 2003503481 20030128
WO 2001002369 20010111
PRIORITY INFORMATION: US 1999-142130 19990702

TITLE: Dosage forms comprising AG013736
INVENTOR(S): Freddo, J.L.; Hu-Lowe, D.; Pithavala, Y.K.; Steinfeldt, H.M.
PATENT ASSIGNEE(S): Pfizer
PATENT INFORMATION: EP 1613320 20060111
US 2004224988 20041111
WO 2004087152 20041014
PRIORITY INFORMATION: US 2003-460695 20030403

Searched by Barb O'Bryen, STIC 2-2518

US 2003-491771 20030731
US 2004-816242 20040401

TITLE: Polymorphic forms of 6-(2-(methylcarbamoyl)phenylsulfanyl)-3-E-(2-(pyridin-2-yl)ethenyl)indazole
INVENTOR(S): Zook, S.E.; Kania, R.S.; Ye, Q.; Ouellette, M.; Hart, R.M.; Wu, Z.P.
PATENT ASSIGNEE(S): Agouron
PATENT ASSIGNEE(S): Pfizer
PATENT INFORMATION: US 2006094763 20060504
WO 2006048751 20060511
PRIORITY INFORMATION: US 2004-624665 20041102
US 2005-264493 20051031

TITLE: Methods for preparing indazole compounds
INVENTOR(S): Dagnino, R. Jr.; Zook, S.E.; Babu, S.; Tian, Q.; Ouellette, M.A.; Shi, B.
PATENT ASSIGNEE(S): Pfizer
PATENT INFORMATION: WO 2006048745 20060511
PRIORITY INFORMATION: US 2004-624575 20041102

TITLE: Methods of preparing indazole compounds
INVENTOR(S): Yu, S.; Srirangam, J.K.; Mitchell, M.B.; Tian, Q.; Shi, B.; Stankovic, N.S.; Ewanicki, B.L.; Flahive, E.J.; Kasparian, A.J.; Perry, M.D.; Sach, N.W.; Saenz, J.E.; O'Neill-Slawecki, S.A.
PATENT ASSIGNEE(S): Agouron
PATENT ASSIGNEE(S): Pfizer
PATENT INFORMATION: US 2006094881 20060504
WO 2006048744 20060511
PRIORITY INFORMATION: US 2004-624635 20041102
US 2005-717071 20050914
US 2005-264440 20051031

REFERENCES:

(1) RefID: 663213, Periodic Publication
"Characterization of potency and activity of the VEGF/PDGF receptor tyrosine kinase inhibitor AG013736"
Hu-Lowe, D.; Hallin, M.; Feeley, R.; et al., Proc Am Assoc Cancer Res (AACR), Vol. 43, (Abst 5356), 2002

(2) RefID: 663215, Periodic Publication
"Pharmacological activities of AG013736, a small molecule inhibitor of VEGF/PDGF receptor tyrosine kinases"
Hu-Lowe, D.; Heller, D.; Brekken, J.; et al., Proc Am Assoc Cancer Res (AACR), Vol. 43, (Abst 5357), 2002

(3) RefID: 739489, Periodic Publication
"AG-013736, a novel VEGFR TK inhibitor, suppresses tumor growth and vascular permeability in human BT474 breast cancer xenografts in nude mice"
Wilmes, L.J.; et al., Proc Am Assoc Cancer Res (AACR), Vol. 44, No. 2nd ed, (Abst 3772), 2003

(4) RefID: 739490, Periodic Publication
"Further characterization of the potent VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736 in preclinical tumor models for its antiangiogenesis and antitumor activity"
Wickman, G.; et al., Proc Am Assoc Cancer Res (AACR), Vol. 44, No. 2nd

ed, (Abst 3780), 2003

(5) RefID: 770180, Periodic Publication
"AG-013736, a potent VEGF/PDGF receptor tyrosine kinase inhibitor, is active against lymphoma growth and chemotherapy-induced vasculogenesis"
Paul, S.; Foutz, T.J.; Calleri, A.; Gobbi, A.; Hu-Lowe, D.; Shalinsky, D.; Bertolini, F., Blood, Vol. 102, No. 11, Part 1, (Abst 2397), 2003

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"A phase I study of the VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736 in patients with advanced solid tumors: Safety, pharmacokinetics, and dceMRI"
Herbst, R.; Rugo, H.; Liu, G.; Park, J.; Kies, M.; Pithavala, Y.; McShane, T.; Evelhoch, J.; Steinfeldt, H.; Reich, S.; Freddo, J.; Wilding, G., AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (15th Edition), Nov 17 2003-Nov 21 2003, Boston, (Abst C253)

(7) RefID: 805000, Periodic Publication
"The discovery of receptor tyrosine kinases: Targets for cancer therapy"
Gschwind, A.; Fisher, O.M.; Ullrich, A., Nat Rev Cancer, Vol. 4, No. 5, pp 361, 2004

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Giles, F.J.; Steinfeldt, H.; Bellamy, W.T.; Bycott, P.; Pithavala, Y.; Reich, S.D.; List, A.F., Blood, Vol. 104, No. 11, Part 1, (Abst 1813), 2004

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Rini, B.; Rixe, O.; Bukowski, R.; et al., Annu Meet Am Soc Clin Oncol (ASCO) (41st Edition), May 13 2005-May 17 2005, Orlando, (Abst 4509)

(10) RefID: 918062, Periodic Publication
"Significant enhancement of anti-tumor efficacy of VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736 in combination with docetaxel in chemo-refractory and/or orthotopic xenograft tumor models in mice"
Hu-Lowe, D.D.; Grazzini, M.L., Proc Am Assoc Cancer Res (AACR), Vol. 46, (Abst 2032), 2005

(11) RefID: 926017, Congress Literature
"Surrogate markers of activity of AG-013736, a multi-target tyrosine kinase receptor inhibitor, in metastatic renal cell cancer (RCC)"
Rixe, O.; Meric, J.-B.; Bloch, J.; Gentile, A.; Mouawad, R.; Adam, V.; Buthiau, D.; Khayat, D., Annu Meet Am Soc Clin Oncol (ASCO) (41st Edition), May 13 2005-May 17 2005, Orlando, (Abst 3003)

(12) RefID: 931236, Periodic Publication
"Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: Results from a phase I study"
Liu, G.; et al., J Clin Oncol, Vol. 23, No. 24, pp 5464, 2005

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"Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: Pharmacokinetic and clinical results"
Rugo, H.S.; et al., J Clin Oncol, Vol. 23, No. 24, pp 5474, 2005

(14) RefID: 931410, Periodic Publication
"PK/PD modeling based on mouse xenograft tumor growth inhibition and the correlation to clinical exposure for VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736"
Yamazaki, S.; Grazzini, M.L.; Romero, D.; Amundson, K.; Pithavala, Y.; Hu-Lowe, D.D., Proc Am Assoc Cancer Res (AACR), Vol. 46, (Abst 3003), 2005

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Frantz, S., Nature, Vol. 437, No. 7061, pp 942, 2005

(16) RefID: 945665, Congress Literature
"A phase I/II study of AG-013736, an oral anti-angiogenesis agent, in combination with docetaxel in patients (pts) with metastatic breast cancer (MBC)"
Rugo, H.S.; et al., Annu San Antonio Breast Cancer Symp (28th Edition), Dec 8 2005-Dec 11 2005, San Antonio, (Abst 1067)

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Ferrara, N.; Kerbel, R.S., Nature, Vol. 438, No. 7070, pp 967, 2005

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Wakelee, H.A.; Schiller, J.H., Clin Lung Cancer, Vol. 7, No. Suppl. 1, pp S31, 2005

(20) RefID: 977848, Periodic Publication
"VHL mutation and response to VEGF pathway-targeted therapy"
Rini, B.I.; et al., Proc Am Assoc Cancer Res (AACR), Vol. 47, (Abst 1283), 2006

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"AG-013736 in combination with gemcitabine versus gemcitabine alone for patients with metastatic pancreatic cancer (NCT00219557)"
ClinicalTrials.gov Web Site, March 20, 2006

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"Phase 2 study of AG-013736 in patients with refractory metastatic renal cell cancer (NCT00282048)"
ClinicalTrials.gov Web Site, April 4, 2006

(23) RefID: 990872, Periodic Publication
"Inhibition of phosphorylation of the colony-stimulating factor-1 receptor (c-Fms) tyrosine kinase in transfected cells by ABT-869 and other tyrosine kinase inhibitors"
Guo, J.; Marcotte, P.A.; McCall, J.O.; Dai, Y.; Pease, L.J.; Michaelides, M.R.; Davidsen, S.K.; Glaser, K.B., Mol Cancer Ther, Vol. 5, No. 4, pp 1007, 2006

(24) RefID: 996603, Company Communication
"AG-013736 in combination with docetaxel versus docetaxel alone for patients with metastatic breast cancer (NCT00076024)"
ClinicalTrials.gov Web Site, May 25, 2006

(25) RefID: 999129, Periodic Publication
"A phase II study of axitinib (AG-013736), a potent inhibitor of VEGFRs, in patients with advanced thyroid cancer"
Kim, S.; et al., J Clin Oncol, Vol. 24, No. 18, Suppl., (Abst 5529), 2006

(26) RefID: 1001146, Periodic Publication
"The anti-angiogenesis agent, AG-013736, has minimal activity in elderly patients with poor prognosis acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)"
Giles, F.J.; Bellamy, W.T.; Estrov, Z.; O'brien, S.M.; Verstovsek, S.; Ravandi, F.; Beran, M.; Bycott, P.; Pithavala, Y.; Steinfeldt, H.; Reich, S.D.; List, A.F.; Yee, K.W., Leuk Res, Vol. 30, No. 7, pp 801, 2006

(27) RefID: 1012866, Company Communication
"Pfizer reports Q2 2006 R&D highlights"
Pfizer Press Release, July 20, 2006

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L23 ANSWER 19 OF 22 PHAR COPYRIGHT 2006 Informa UK Ltd on STN
AN 30611 PHAR
DN 036322
CN axitinib
CN AG-013736
CN CP-868596
CN N-methyl-2-((3-((1E)-2-(pyridin-2-yl)ethenyl)-1H-indazol-6-yl)sulfanyl)benzamide
RN **319460-85-0**
MF C22 H18 N4 O S
MW 386.47
HAC 4
HD 2
LOGP 3.87
FRB 6
STA Active

CO

Type	Company Name (Country)	Development Status
Originator	OSI Pharmaceuticals (United States)	Phase II Clinical Trial
Licensee	Pfizer (United States)	Phase II Clinical Trial

SO Pharmaprojects. PJB Publications, T&F Informa UK Ltd, London
TX Axitinib (AG-013736; CP-868596) is a small-molecule, orally available VEGF/PDGF receptor tyrosine kinase inhibitor under development by OSI

Pharmaceuticals and Pfizer for the treatment of cancer.

Marketing

Axitinib was discovered through a collaboration between OSI and Pfizer.

Clinical

Phase II

In a multicentre Phase II trial in 52 metastatic renal cell cancer (RCC) patients, who had previously failed cytokine-based therapy, axitinib 5mg was well tolerated and had a significant objective response rate. Partial response to treatment was 46% and stable disease was experienced by 40% of patients, with a median follow-up of 12mth. No moderate or severe myelosuppression was observed; however, 31% had progressive disease, 13% have withdrawn due to adverse events and 1 PR patient relapsed. It is in Phase II trials for metastatic melanoma, refractory thyroid cancer and nsclc, as well as in combination with docetaxel in breast cancer (41st ASCO (Orlando), 2005).

Preclinical

In preclinical xenograft models, axitinib po bid inhibited angiogenesis, tumour growth and metastasis. Greater antitumour efficacy was achieved with co-administration with docetaxel cf either agent alone. In mice, t1/2 was 2hr and maximal antitumour efficacy was achieved with po administration once-daily (94th AACR (Washington, DC), 2003, Abs 3772 and 3780). Updated by LK on 28/6/2005.

DSTA World: Phase II Clinical Trial
United States: Phase II Clinical Trial
CC K6Z Anticancer, other
CT Indication: Cancer, renal (Phase II Clinical Trial); Cancer, breast (Phase II Clinical Trial); Cancer, melanoma (Phase II Clinical Trial); Cancer, lung, non-small cell (Phase II Clinical Trial); Cancer, thyroid (Phase II Clinical Trial)
GEN LOCUSID: 3791. Target Gene: kinase insert domain receptor (a type III receptor tyrosine kinase)
Synonyms: KDR; FLK1; VEGFR2; VEGF receptor-2 tyrosine kinase; VEGFR-2 tyrosine kinase; vascular endothelial growth factor receptor 2
GEN LOCUSID: 5156. Target Gene: platelet-derived growth factor receptor, alpha polypeptide
Synonyms: PDGFRA; CD140a; PDGFR2; PDGFR kinase, bcr fusion-linked; PDGFR/bcr fusion, PDGFR component; PDGF receptor kinase, bcr fusion-linked; platelet-derived growth factor receptor tyrosine kinase, bcr fusion-linked; PDGFR alpha; PDGF receptor alpha; MGC74795
ORGM CH-SY (Chemical, synthetic)
RTE A-PO (Alimentary, po)
RDAT 20050628 RNTE ##Actual; New Chemical Structure New
20050628 ##Estimated; Names Granted AG-013736
20050515 ##Estimated; Change in Status Phase II Clinical Trial
20050515 ##Estimated; New Indication Cancer, breast, melanoma, thyroid, nsclc and renal
20040517 ##Actual; Change in Status Phase I Clinical Trial
20030716 ##Actual; New Product in Pharmaprojects
NRAT 5:Novelty Rating - 2nd, 3rd or 4th Compound
MRAT 3:Market Rating - US$ 2001-5000 million

SRAT 4:Speed Rating - Faster than Average
TRAT 12:Total Rating - Total Rating
PHCD KI-GFEN-AN; Endothelial growth factor receptor kinase inhibitor; Enzyme, Transferase, Endothelial growth factor receptor kinase inhibitor; VEGFR kinase inhibitor; VEGF receptor tyrosine kinase inhibitor; E-TR-KI-GFEN-AN.
PHCD KI-GFPL-AN; Platelet-derived growth factor receptor kinase inhibitor; Enzyme, Transferase, Plateletderived growth factor receptor kinase inhibitor; Platelet-derived growth factor kinase inhibitor; PDGF receptor kinase inhibitor; PDGF kinase inhibitor; E-TR-KI-GFPL-AN; 2.7.1.
PHCD E; E-TR; E-TR-KI; E-TR-KI-GFEN; E-TR-KI-GFEN-AN; E-KI; E-KI-GFEN; E-KI-GFEN-AN; E-GFEN; E-GFEN-AN; E-AN; TR; TR-KI; TR-KI-GFEN; TR-KI-GFEN-AN; TR-GFEN; TR-GFEN-AN; TR-AN; KI; KI-GFEN; KI-GFEN-AN; KI-AN; GFEN; GFEN-AN; E-TR-KI-AN; E-KI-AN; TR-KI-AN; E-TR-AN; E-TR-KI-GFPL; E-TR-KI-GFPL-AN; E-KI-GFPL; E-KI-GFPL-AN; E-GFPL; E-GFPL-AN; TR-KI-GFPL; TR-KI-GFPL-AN; TR-GFPL; TR-GFPL-AN; KI-GFPL; KI-GFPL-AN; GFPL; GFPL-AN.

LN

Therapy (CC)	Pharmacology (PHCD)	Status (DSTC)
K6Z	KI-GFEN-AN KI-GFPL-AN	C2

LCDAT 20050628: LK : Granting of USAN and chemical structure reported

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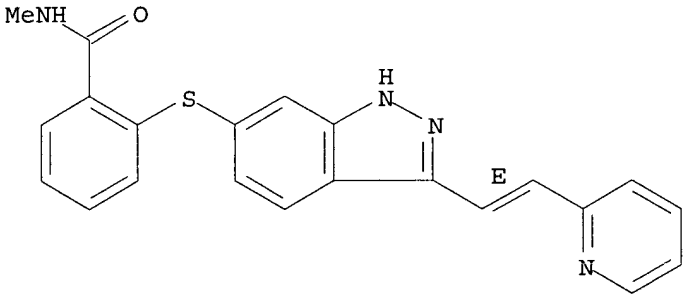
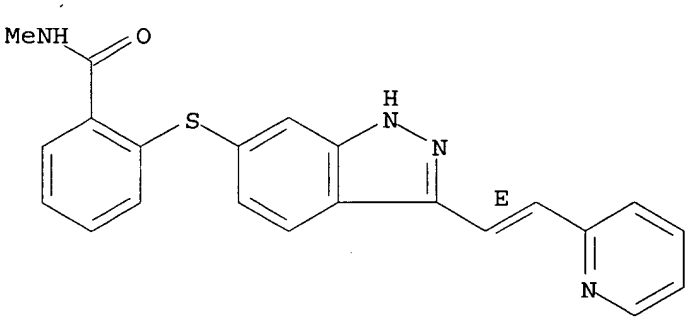


L23 ANSWER 20 OF 22 ADISINSIGHT COPYRIGHT (C) 2006 Adis Data Information BV on STN
ACCESSION NUMBER: 2002:507 ADISINSIGHT
SOURCE: Adis R&D Insight
DOCUMENT NO: 017408
CHANGE DATE: Jun 27, 2006
GENERIC NAME: Axitinib
SYNONYM: AG 013736; AG 13736; AG-13;736
CHEMICAL NAME: N-Methyl-2-((3-((1E)-2-(pyridin-2-yl)ethenyl)-1H-indazol-6-yl)sulfanyl)benzamide
MOLECULAR FORMULA: C22 H18 N4 O S

Searched by Barb O'Bryen, STIC 2-2518

CAS REGISTRY NO.: **319460-85-0**
STRUCTURE:

Double bond geometry as shown.



EPHMRA ATC CODE: L1 Antineoplastics
WHO ATC CODE: L01 Antineoplastic Agents
HIGHEST DEV. PHASE: Phase II

CURRENT DEVELOPMENT STATUS:
Phase II, United States, Solid tumours
Phase I, United States, Breast cancer

COMPANY INFORMATION
ORIGINATOR: Pfizer (United States)
PARENT: Pfizer

OTHER SOURCES: 801029751; 800883358; 801011782
WORD COUNT: 756

TEXT
Introduction:
Pfizer is developing axitinib (AG 013736, AG 13736), a small molecule inhibitor of vascular endothelial growth factor receptor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases. It may have potential in the treatment of a variety of solid tumour types.

Key development milestones
In November 2004, Pfizer initiated a phase II study of axitinib in solid tumour patients with breast and renal cancers/1/.

Pfizer has conducted a phase I, dose-escalation study of axitinib in 30 patients with advanced solid tumours. Pfizer presented the results of the study at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2003) in November 2003.

COMMERCIAL SUMMARY:
Cancer / VEGF receptor inhibitor

Company	Region	Launch Date	Peak Sales	Patent Expiry
Pfizer	Wrld	2009	$750m	

PHARMACOLOGY OVERVIEW:
Antimicrobial activity:

Pharmacodynamics:
Produces dose-dependent inhibition of human colorectal cancer xenografts; inhibits metastasis to lymph nodes and lung in an orthotopic melanoma model; decreases tumour vascular response; enhances tumour growth delay when co-administered with docetaxel in mice
Mechanism of action:
Platelet-derived growth factor receptor tyrosine kinase inhibitors
Tyrosine kinase inhibitors
Platelet-derived growth factor antagonists
Protein kinase inhibitors
Growth factor antagonists
Kinase inhibitors
Enzyme inhibitors
Vascular endothelial growth factor agonists
Growth factor agonists
Angiogenesis inhibitors
Activity versus parent drug: unspecified parent

CLINICAL OVERVIEW:
Route(s) of Administration: PO
Administration Freq.(per day):
Adverse events:
occasional: Anaemia, Neutropenia.
Drug Interactions:
Unknown.

Adverse Events:
Preclinical studies: in xenografts tumour models in mice, co-administration of axitinib and docetaxel was well tolerated in general, although a slight increase in bodyweight loss was noted in the combination group, compared with those treated with axitinib alone/2/.

Clinical studies: the dose-limiting toxicity (DLT) associated with axitinib at doses <= the mean tolerated dose (MTD) (5mg BD in fed patients) was grade 1 stomatitis, which was observed in one patient treated in the phase I, dose-escalation study conducted in 30 patients with advanced solid tumours. Non-dose-limiting hypertension, which was manageable with regular antihypertensive therapy, was observed in 5/12 patients. DLTs in patients treated with > the MTD were hypertension, seizures, elevated liver enzymes, pancreatitis, apnea, and stomatitis. Fatal hemotysis was also observed in two responding patients with non-small cell lung cancer, one case was 3 weeks after treatment was stopped. Non-dose limiting proteinuria was also observed/3/.
In a phase I/II trial of axitinib in combination with docatexel, the major adverse events were grade 3/4 neutropenia (n=3) and grade 3/4 anaemia (3)/4/.
Drug Interactions:

PHARMACOLOGY:
Pharmacokinetics:
Axitinib exhibited variable (39-96% CV) but linear plasma pharmacokinetics in a phase I, dose-escalation study conducted in 30 patients with advanced solid tumours. Axitinib was administered orally once or twice daily on a 28 days cycle. Peak concentrations of the drug were observed 2-4 hours post-dose. The terminal plasma t sub(1/2) was 3-5 hours. Fasted patients (no food/beverages within 2 hours of dosing) had approximately 49% higher plasma exposure levels compared with fed patients. Intra-patient variability was also reduced in fasted versus fed patients. The C sub(max) and AUC on day 15 were 54.5 ng/mL

and 311 ng x h/mL, respectively, in fed patients treated with axitinib 5mg twice daily/3/.

Plasma profiles and PK values of axitinib were not influenced by the addition of docataxel to the therapeutic regimen for patients with metastatic breast cancer/4/.

Pharmacodynamics (Cancer):

Preclinical studies: axitinib produced dose-dependent inhibition of human MV522 colon cancer xenografts and Lewis lung cancer tumour in mice, with an ED sub(50) of 1.2 mg/kg twice daily. It also inhibited metastasis to the lymph nodes and lung in an orthotopic melanoma model/5/.

Significant enhancements in tumour growth delay were observed in vivo when axitinib (3-30 mg/kg, orally administered twice daily) was co-administered with docetaxel (40 mg/kg, administered intravenously once weekly), compared with axitinib alone or docetaxel alone (100%, 65% and 9% in the respective treatment groups). In addition, survival was prolonged following co-administration of axitinib (30 mg/kg) and docetaxel (40 mg/kg), compared with each agent alone (86% vs 23%)/2/.

Clinical studies: acute decreases in tumour vascular response (>= 50% decrease in K sup(trans) and the initial area under the contrast intensity X time curve (IAUC)) were observed in 6/18 evaluable patients in a trial using dceMRI. In addition, 11/18 patients demonstrated a >= 40% decrease in both IAUC and K sup(trans). The patients were enrolled in a phase I, dose-escalation study conducted in 30 patients with advanced solid tumours/3/.

THERAPEUTIC TRIALS:

Cancer:

The mean tolerated dose of axitinib was found to be 5mg twice daily in fed patients in a phase I, dose-escalation trial conducted in 30 patients with advanced solid tumours.

Renal cancer:two durable partial responses (assessed by RECIST criteria) were observed in patients with renal cancer and adenoid cystic carcinomas. Stable disease lasting 4 months to more than 13 months was also observed in 5 heavily pretreated patients/3/.

In a phase II study, axitinib had promising efficacy in patients with cytokine-refractory metastatic renal cell carcinoma. Forty-six percent of patients achieved a partial clinical response and 40% had stable disease. The median time to disease progression was not reached after 12-18 months of follow-up/6/.

Breast cancer: treatment with axitinib + docetaxel resulted in partial responses in 2 patients and stable disease in 3 for >= 4 months. Stable disease/response was maintained in 3 patients with single-agent axitinib after treatment with the combination therapy/4/.

REFERENCES

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2. Hu-Lowe DD, Grazzini ML. Significant enhancement of anti-tumor efficacy of VEGF/PDGF receptor tyrosine kinase inhibitor AG-013736 in combination with docetaxel in chemo-refractory and/or orthotopic xenograft tumor models in mice. 96th Annual Meeting of the American Association for Cancer Research. 46: 475-476, Apr 2005. (English).
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anti-angiogenesis agent, in combination with docetaxel in patients with metastatic breast cancer. Breast Cancer Research and Treatment. 94 (Suppl. 1): 62 (plus poster) abstr. 1067, 2005. (English). 801029751
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6. Rini B, Rixe O, et al. AG-013736, a multi-target tyrosine kinase receptor inhibitor, demonstrates anti-tumor activity in a phase 2 study of cytokine-refractory, metastatic renal cell cancer. Journal of Clinical Oncology. 23 (Suppl.): 380 (plus oral presentation) abstr. 4509, No. 16, Part I, 1 Jun 2005. (English). 801011782

L23 ANSWER 21 OF 22 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-253267 [26] WPIX
CROSS REFERENCE: 2006-293183 [30]; 2006-293404 [30]
DOC. NO. CPI: C2006-082484
TITLE: Pharmaceutical composition, useful for the prevention and treatment of cancer, comprises sulfonamide compound and angiogenesis inhibitor.
DERWENT CLASS: B05
INVENTOR(S): OWA, T; OZAWA, Y; SEMBA, T
PATENT ASSIGNEE(S): (EISA) EISAI CO LTD
COUNTRY COUNT: 111
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006030947	A1	20060323	(200626)*	JA	258	A61K031-403

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006030947	A1	WO 2005-JP17238	20050913

PRIORITY APPLN. INFO: JP 2005-54475 20050228; US 2004-609452P 20040913; JP 2005-54150 20050228
INT. PATENT CLASSIF.:
MAIN: A61K031-403; A61K031-404
SECONDARY: A61K031-18; A61K031-381; A61K031-498; A61K031-63; A61K031-635; A61K031-64; A61K039-395; A61K045-00; A61P009-00; A61P035-00
BASIC ABSTRACT:
WO2006030947 A UPAB: 20060510
NOVELTY - A pharmaceutical composition comprises one or more sulfonamide compound (A) of specified formula and a component (B) which inhibits

angiogenesis.

DETAILED DESCRIPTION - A pharmaceutical composition comprises one or more sulfonamide compound (A) of specified formula and a component (B) which inhibits angiogenesis.

(A) is one or more compound of formula (I)-(IV) or their salts or solvates.

E = O, N(CH3), CH2, CH2CH2, or CH2O;
D = CH2 or O;
R1a = H or halo;
R2a = halo or CF3;
J = O or NH;

R1b = H, halo, nitro, azido, OSO2CH3, N(CH3)2, OH, pyridyl, thienyl, furyl, quinolinyl or triazole; or 1-6C alkyl, 1-4C alkoxy, 1-4C alkylthio, 2-5C alkoxycarbonyl or phenyl (all optionally substituted);

R2b = H, halo, CN, or 1-6C alkyl, 1-4C alkoxy, 2-5C alkoxycarbonyl, phenyl or quinolinyl (all optionally substituted);

R3b = H or optionally substituted 1-4C alkoxy;

R4b = H or 1-6C alkyl (provided that at least one of R3b and R3c is H);

R5b = H, halo, optionally substituted 1-6C alkyl or NO2;

R6b = H, halo, or 1-6C alkyl (provided that when R6b is optionally substituted 1-6C alkyl, then R5b is H and R7b is halo)

R7b = halo or optionally substituted 1-6C alkyl (provided that when one of R5b and R7b is optionally substituted 1-6C alkyl, or R7b is halo or optionally substituted 1-6C alkyl, then one of R5b and R6b is H).

INDEPENDENT CLAIMS are also included for:

(1) pharmaceutical compositions comprising:

(a) a combination of a sulfonamide compound of formula (IX) or its salts or solvates and (B);

(b) a combination of a sulfonamide compound of formula (XIV) or its salts or solvates and one of 19 named VEGF receptor kinase inhibitor compounds (B10)-(B28);

(c) a combination of (IX) and the VEGF receptor kinase 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinoline carboxamide (B') or its salt or solvate; and

(d) a pharmaceutical composition containing a sulfonamide compound (I)-(IV), (IX) or (XIV) for administration together with a angiogenesis inhibitor;

(2) A kit containing at least one of a package container, explanation sheet and package insert sheet which record the combined use of (A) and (B); and

(3) A kit containing a set formed of a formulation containing (A) and a formulation containing (B).

Ring A = optionally substituted mono- or bi- cyclic aromatic ring;

Ring B = optionally substituted 6-membered ring which is unsaturated carbocycle or containing 1 N as heteroatom;

Ring C = optionally substituted 5-membered heterocycle containing 1-2N;

W = bond or CH=CH;
X = N(R1) or O;
Y = C(R3) or N;
Z = NR2;

R1-R3 = H or lower alkyl;

ACTIVITY - Cytostatic; Antiangiogenic.

Cells of the human kidney cancer strain 786-O were transplanted subcutaneously into nude mice. After 7 days, the mice were treated with 100mg/kg N-(3-cyano-4-methyl-1H-indol-7-yl)-3-cyanobenzene sulfonamide (E7820) twice daily and/or 100 mg/kg 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinoline carboxamide (B') once daily for 2 weeks. The volume of the tumors was measured at the

start of treatment and at the end of treatment, (day 22), and the ratio (volume at end of treatment)/(volume at start of treatment) was determined. Ratio was 1.61 for untreated control; 0.80 with E7820 alone; 0.59 with (B') alone; and 0.16 with E7820 + (B'); p less than 0.01 (calculated by two-way ANOVA).

MECHANISM OF ACTION - VEGF receptor kinase inhibitor; FGF receptor kinase inhibitor.

USE - The combinations and kits are used as a method of inhibiting angiogenesis and treating cancer (claimed), in the prevention, treatment, prevention of recurrence, and inhibition of metastasis of cancer, including carcinoma, myoma and melanoma, in mammals including humans. IMC-1121b, IMC-18F1, IMC-1C11 and IMC-2C6.

ADVANTAGE - The combinations have synergistic effect.

Dwg.0/8

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-G04; B04-G21; B06-H; B07-B01; B07-D04C; B10-A08; B10-A13D; B14-D06C; B14-F02F2; B14-H01; B14-S09; B14-S18
TECH UPTX: 20060421

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred composition: (B) is a VEGF receptor kinase inhibitor or FGF receptor kinase inhibitor.

L23 ANSWER 22 OF 22 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-701891 [72] WPIX
DOC. NO. CPI: C2005-213419
TITLE: Treatment of abnormal cell growth e.g. cancer involves administering a combination of selective cyclin-dependent kinase inhibitor and at least one signal transduction inhibitor.
DERWENT CLASS: B05
INVENTOR(S): ECK, S L; FRY, D W; LEOPOLD, J A; LEOPOLD, J A S
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (PFIZ) PFIZER PROD INC
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2005222163	A1	20051006	(200572)*		31	A61K031-519
WO 2005094830	A1	20051013	(200572)	EN		A61K031-519

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005222163	A1 Provisional	US 2004-557623P	20040330
		US 2005-95442	20050330
WO 2005094830	A1	WO 2005-IB720	20050318

PRIORITY APPLN. INFO: US 2004-557623P 20040330; US 2005-95442 20050330

INT. PATENT CLASSIF.:
MAIN: A61K031-519
SECONDARY: A61K031-166; A61P035-00
BASIC ABSTRACT:
US2005222163 A UPAB: 20051109
NOVELTY - Treating abnormal cell growth in a patient involves administering a combination of selective cyclin-dependent kinase (CDK) inhibitor and at least one signal transduction inhibitor.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido(2,3-d)pyrimidin-7-one (A1) or its isethionate salt and at least one signal transduction inhibitor selected from tyrosine kinase inhibitors, mitogen-activated protein kinase (MAP)/extracellular signal regulated kinase (ERK) (MEK) inhibitors, bcr-abl tyrosine kinase inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, c-Kit inhibitors, erbB inhibitors, vasculature epidermal growth factor receptor (VEGF-R) inhibitors, 90-kDa heat shock protein (Hsp 90) inhibitors, Aurora kinase inhibitors, Fms-like tyrosine kinase-3 (FLT-3) inhibitors, n-Ras inhibitors, phosphatidylinositol-3 (PI3) kinase inhibitors, Raf kinase inhibitors, Akt inhibitors, mammalian targret of rapamycin (mTOR) inhibitors and/or multitargeted kinase inhibitors.

ACTIVITY - Cytostatic; Neuroprotective; Vasotropic; Antiinflammatory; Angiogenesis-inhibitor. Test details are described but no results are given.

MECHANISM OF ACTION - Tumor cell growth inhibitor.

USE - For treating abnormal cell growth in a patient (claimed), for treating cancer e.g. lung cancer, bone cancer, ovarian, breast or skin cancer; also for treating other disorders e.g. neuronal, glial, glandular, macrophagal or epithelial disorders, restenosis, or inflammatory, angiogenic and immunological disorders.

ADVANTAGE - The combination of CDK inhibitor and signal tranduction inhibitors produces a direct effect on the signaling pathways that promote growth, proliferation and survival of a cell and is effective in treating abnormal cell growth, preferably cancer.

Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-B; B02-D; B04-B03D; B05-A03B; B05-B01J; B06-H; B07-H; B10-A10; B10-A13D; B10-A18; B10-B03B; B14-C03; B14-F01; B14-F02; B14-G03; B14-H01; B14-J01
TECH UPTX: 20051109
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compositions: When the CDK inhibitor is CDK-4/6 inhibitor (A1), then the signal transduction inhibitor(s) is selected from MEK inhibitor; or Raf kinase inhibitor, Akt inhibitor and/or mTOR inhibitor; or Raf kinase or mTOR inhibitor; or bcr-abl tyrosine, PDGF-R, c-Kit, erbB, VEGF-R, FGFR and/or IGF1-R inhibitor; or PDGFR, erbB, or VEGF-R inhibitor; or multi-targeted kinase inhibitor. Preferred Components: The CDK inhibitor is CDK-4, CDK-6 or CDK4/6 inhibitor. CDK-4/6 inhibitor is (A1). MEK inhibitor is selected from 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide or N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide. Raf kinase or mTOR inhibitor is selected from BAY 43-9006, rapamycin, CCI 779, Rad001 or Arry 142886. PDGFR, erbB, or VEGF-R inhibitor is selected from CP-868596, ST-1571, PTK-787, PKC-412, Herceptin (trastuzumab), Erbitux, Iressa (gefitinib), Tarceva (erlotinib), EKB-569, PKI-166, GW-572016, E-2-methoxy-N-(3-(4-(3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino)-quinazolin-6-yl)-allyl)-acetamide, CI-1033, CP-547632, ZD-6474, or Avastin (Bevacizumab). A multi-targeted kinase inhibitor is SU11248 or Gleevec. Preferred Method: The method further involves

administering at least one additional therapeutic agent selected from an antitumor agent, alkylating agent, antimetabolite, antibiotic, plant-derived antitumor agent, camptothecin derivative, interferon or a biological response modifier (preferably cis-platin, oxaliplatin, carboplatin, cyclophosphamide, 5-fluorouracil, capecitabine, cytosine, arabinosid, hydroxyurea, N-(5-(N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino)-2-thenoyl)-L-glutamic acid, adriamycin, bleomycin, interferon, nolvadex (tamoxifen), or casodex (4'-cyano-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide).

FILE 'HOME' ENTERED AT 12:25:15 ON 10 AUG 2006

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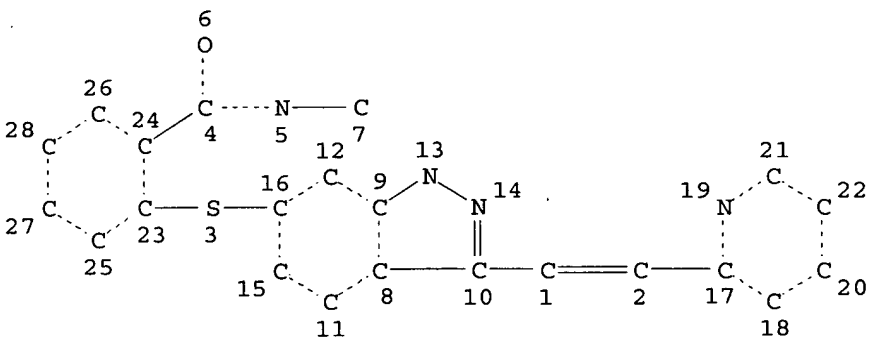
=> d stat que l7; d his nofile
L5 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 28

STEREO ATTRIBUTES: NONE
L7 3 SEA FILE=REGISTRY FAM FUL L5

100.0% PROCESSED 21 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

(FILE 'HOME' ENTERED AT 12:08:47 ON 10 AUG 2006)

FILE 'CAPLUS' ENTERED AT 12:08:54 ON 10 AUG 2006
E US2004-816242/APPS
L1 1 SEA ABB=ON US2004-816242/AP
D SCAN
SEL RN

FILE 'REGISTRY' ENTERED AT 12:09:30 ON 10 AUG 2006
L2 5 SEA ABB=ON (108334-68-5/BI OR 114977-28-5/BI OR 319460-85-0/BI
OR 771570-72-0/BI OR 80449-01-0/BI)
D SCAN
L3 2 SEA ABB=ON L2 AND BENZAMIDE
D SCAN
L4 1 SEA ABB=ON L2 AND C22 H18 N4 O S/MF
D IDE
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L6 0 SEA FAM SAM L5
L7 3 SEA FAM FUL L5
SAVE TEMP L7 GEM242FAM/A

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L8 17 SEA ABB=ON L7

FILE 'STNGUIDE' ENTERED AT 12:13:04 ON 10 AUG 2006

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     10 AUG 2006
L9            44 SEA ABB=ON  FREDDO J?/AU
L10         2512 SEA ABB=ON  HU LOWE D?/AU OR HULOWE D?/AU OR LOWE D?/AU
L11           81 SEA ABB=ON  KERSI PITHAVALA Y?/AU OR PITHAVALA Y?/AU
L12           17 SEA ABB=ON  STEINFELDT H?/AU
L13            1 SEA ABB=ON  L9 AND L10 AND L11 AND L12
L14           13 SEA ABB=ON  (L9 AND (L10 OR L11 OR L12)) OR (L10 AND (L11 OR
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     10 AUG 2006
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                D QUE L1

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                       ANSWERS '2-4' FROM FILE MEDLINE
                       ANSWERS '5-8' FROM FILE DRUGU
                       ANSWER '9' FROM FILE BIOSIS
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                  D IALL 2-9

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                D STAT QUE L7
                D IDE L7 1-3

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                SET TERMSET E#
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L16             1 SEA ABB=ON  319460-85-0/RN
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                  SET LINE LOGIN
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                  D SCAN
                  D TRIAL

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     FILE 'CAPLUS' ENTERED AT 12:21:01 ON 10 AUG 2006
L18            17 SEA ABB=ON  L7
L19            16 SEA ABB=ON  L18 NOT L1

     FILE 'IPA, TOXCENTER, PROUSDDR, PHAR, ADISINSIGHT' ENTERED AT 12:21:34 ON
     10 AUG 2006
L20            19 SEA ABB=ON  L7

     FILE 'WPIX' ENTERED AT 12:21:49 ON 10 AUG 2006
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L21             1 SEA ABB=ON  AXITINIB/CN
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L22          11 SEA ABB=ON  RA3G48/DCN OR 366778-0-0-0/DCRE OR AXITINIB/BI,ABEX
                 OR AG013736/BI,ABEX OR AG 013736/BI,ABEX
               D TRIAL 1-11

     FILE 'WPIX' ENTERED AT 12:24:12 ON 10 AUG 2006
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     FILE 'CAPLUS, IPA, TOXCENTER, PROUSDDR, PHAR, ADISINSIGHT, WPIX' ENTERED
     AT 12:24:22 ON 10 AUG 2006
L23          22 DUP REM L19 L20 L22 (24 DUPLICATES REMOVED)
                    ANSWERS '1-16' FROM FILE CAPLUS
                    ANSWER '17' FROM FILE TOXCENTER
                    ANSWER '18' FROM FILE PROUSDDR
                    ANSWER '19' FROM FILE PHAR
                    ANSWER '20' FROM FILE ADISINSIGHT
                    ANSWERS '21-22' FROM FILE WPIX
               D IBIB ED ABS HITSTR 1-16
               D IALL 17-18
               D ALL 19
               D IALL 20
               D IALL ABEQ TECH 21-22

     FILE 'HOME' ENTERED AT 12:25:15 ON 10 AUG 2006
               D STAT QUE L7

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